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Improving aneurysmal subarachnoid hemorrhage management, what's new?

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Improving aneurysmal subarachnoid hemorrhage management, what's new?

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Editorial: Improving aneurysmal Subarachnoid hemorrhage management, what's new?

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Editorial on the Research Topic
Improving aneurysmal Subarachnoid hemorrhage management, what's new?

Despite significant progress in critical care, aneurysmal subarachnoid hemorrhage (aSAH) still represents a severe form of stroke with a high mortality rate.

Prehospital mortality rates for aSAH range from 22% to 26%. Although hospital mortality rates have shown stability (13.7% in 2006 to 13.1% in 2018 (United States) (1) and 19%−20% in 2021 (global) (2), population-based studies indicate a decline in the overall case-fatality rates (−1.5%/year between 1980 and 2020) albeit with substantial inter-country variability (3, 4).

While aSAH incidence varies between populations, nearly half of all survivors experience some level of persistent neurological deficit. This burden is particularly high because, unlike other types of stroke, aSAH affects patients in their working years, with a mean age of 55 years (1). Moreover, aSAH imposes significant economic costs, with estimated inpatient hospital charges ranging from $373 353.94 to $530 544.77 [for those individuals with aSAH who develop delayed cerebral ischemia (DCI)] in the United States (5).

Managing aSAH is a multidisciplinary challenge that extends beyond treating and securing the bleeding aneurysm, as outcomes are influenced by complications like vasospasm, hydrocephalus, and delayed ischemic deficit.

The main purpose of this Research Topic was to gather publications that focus on the advancement and update of management criteria and therapeutic strategies to improve the daily multidisciplinary care of aSAH.

When this Research Topic was issued, the most recent available guidelines dated back to 2012 and covered literature up to May 2010 (A revision, from a European standpoint, was provided by the Guidelines Committee of the European Stroke Organization in 2013) (6, 7).

The new aSAH management guidelines published by the American Heart Association/American Stroke Association in June 2023 (8) have updated many recommendations based on new evidence, although some controversy persists.

For instance, it is globally accepted that nimodipine is a mainstay of treatment after aneurysmal subarachnoid hemorrhage, as it has been shown to reduce the risk of delayed cerebral ischemia with consequent improved functional outcomes after aSAH. Therefore, guidelines advocate early initiation of enteral nimodipine. However recent studies suggest individual variability in its absorption in aSAH patients, potentially affecting the prognosis (Mahmoud et al.).

Despite advances, in-hospital mortality and severe disability rates in aSAH patients remain of concern, with a subset of patients at higher risk of complications and poor outcomes (Liu et al.; Liu and Wang; Bögli et al.; Scibilia et al.).

There is growing interest in recognizing sex-specific extra-cerebral complications, which could lead to the development of more tailored monitoring and therapeutic strategies to reduce mortality and disability from aSAH.

For example, it has been reported that women appear to be at greater risk of cardiac and infectious complications than men, and, together with patients with a history of cardiac disorders, they may benefit from personalized management when at risk for symptomatic vasospasm/DCI. In these patients, either a closer evaluation for a new cardiac injury or possibly lower blood pressure targets should be therefore considered (Bögli et al.).

In a retrospective study by Hu, age, blood glucose (>7.22 mmol/L), Glasgow Coma Scale, and red blood cell distribution width-SD were proven to be independent risk factors for hospital-acquired pneumonia in aSAH patients (HAP) (Hu et al.). In this respect, it has been previously reported that HAP in aSAH is associated with worse long-term outcomes as respiratory complications compromise air exchange and aggravate hypoxia, worsening brain injury (9).

Early identification of higher-risk aSAH patients could facilitate the application of individualized management and treatment strategies to improve outcomes and reduce the social costs of this devastating disease. Integration of these considerations into the emergency care of low grade aSAH patients, along with clinical and anamnestic information, may support the multidisciplinary neurovascular team in making clinical decisions and engaging in realistic discussions with patients' caregivers.

While progress has been made, several aspects continue to challenge us. Despite a seeming decline in the overall incidence and prevalence of aSAH, persistently high in-hospital and prehospital mortality rates and an increased incidence in the elderly population require refinement of therapies and practice standards for the management of aSAH patients and, hopefully, non-invasive and low-cost tests to better identify patients at high risk for poor outcomes.

Advancements in the diagnostic process, management strategies, and understanding of the complex mechanism of injury following aSAH hold promise for improving patient prognosis in the future.

Author contributions

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A predictive model using risk factor categories for hospital-acquired pneumonia in patients with aneurysmal subarachnoid hemorrhage

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Objectives: To identify risk factors for hospital-acquired pneumonia (HAP) in patients with aneurysmal subarachnoid hemorrhage (aSAH) and establish a predictive model to aid evaluation.

Methods: The cohorts of 253 aSAH patients were divided into the HAP group ($n = 64$) and the non-HAP group ($n = 189$). Univariate and multivariate logistic regression were performed to identify risk factors. A logistic model (Model-Logit) was established based on the independent risk factors. We used risk factor categories to develop a model (Model-Cat). Receiver operating characteristic curves were generated to determine the cutoff values. Areas under the curves (AUCs) were calculated to assess the accuracy of models and single factors. The Delong test was performed to compare the AUCs.

Results: The multivariate logistic analysis showed that the age [$p = 0.012$, odds ratio (OR) = 1.059, confidence interval (CI) = 1.013–1.107], blood glucose (BG; >7.22 mmol/L; $p = 0.011$, OR = 2.781, CI = 1.263–6.119), red blood distribution width standard deviation (RDW-SD; $p = 0.024$, OR = 1.118, CI = 1.015–1.231), and Glasgow coma scale (GCS; $p < 0.001$, OR = 0.710, CI = 0.633–0.798) were independent risk factors. The Model-Logit was as follows: Logit(P) = −5.467 + 0.057 * Age + 1.023 * BG (>7.22 mmol/L, yes = 1, no = 0) + 0.111 * RDW-SD−0.342 * GCS. The AUCs values of the Model-Logit, GCS, age, BG (>7.22 mmol/L), and RDW-SD were 0.865, 0.819, 0.634, 0.698, and 0.625, respectively. For clinical use, the Model-Cat was established. In the Model-Cat, the AUCs for GCS, age, BG, and RDW-SD were 0.850, 0.760, 0.700, 0.641, and 0.564, respectively. The AUCs of the Model-Logit were insignificantly higher than the Model-Cat (Delong test, $p = 0.157$). The total points from −3 to 4 and 5 to 14 were classified as low- and high-risk levels, respectively.

Conclusions: Age, BG (> 7.22 mmol/L), GCS, and RDW-SD were independent risk factors for HAP in aSAH patients. The Model-Cat was convenient for

practical evaluation. The aSAH patients with total points from 5 to 14 had a high risk for HAP, suggesting the need for more attention during treatment.

KEYWORDS

aneurysmal subarachnoid hemorrhage, hospital-acquired pneumonia (HAP), predictive model, risk factor, age, Glasgow coma scale (GCS), blood glucose, red blood cell width distribution standard deviation

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a neurologic emergency associated with a 32%−67% mortality and many severe complications (1, 2). About one-third of aSAH patients suffer from systemic infections (predominantly pneumonia) that can contribute to excess mortality after SAH (2, 3). Hospital-acquired pneumonia (HAP) is a common complication associated with poor outcomes (4–6). Even though numerous studies focused on stroke-associated pneumonia and acquired clinically predictive scales (7–9), different types of the stroke influenced the occurrence of HAP and reduced the prediction accuracy (10). To further specifically evaluate the HAP factors in aSAH patients and create strategies to prevent HAP and improve outcomes, it is critical to identify and mitigate risk factors in aSAH patients (4, 11).

Studies focusing on HAP in patients with aSAH returned inconsistent results. Chen et al. (11) demonstrated the significance of the neutrophil-to-lymphocyte ratio (NLR) in 711 aSAH patients. Wang et al. found that risk factors for pneumonia in aSAH patients included advanced age, male sex, weekend admission, the World Federal Neurological Society (WFNS) grade, extensive enteral nutrition, endovascular treatment, and specific laboratory parameters (4). Some studies only tested their limited cohorts' accuracy and thresholds of associated risk factors (12, 13). Nevertheless, clinical work requires a valid and convenient model to predict HAP in aSAH patients. Therefore, we explored the risk factors for HAP in patients with aSAH and established a predictive model.

Methods

Patients

The flow chart of patient selection is shown in Figure 1. Our hospital's institutional ethics committee approved this study. We collected data after obtaining the consent of the patients or their close relatives. From January 2020 to January 2022, 308 patients were diagnosed with SAH identified by computed tomography. There were 288 patients with a definitive diagnosis of an intracranial aneurysm according to computerized tomography angiography, digital subtraction angiography, or surgery at our institute (20 patients were excluded for non-aneurysmal hemorrhages). Exclusion criteria were as follows: (1) the interval between the bleeding and admission exceeded 48 h ($n = 7$); (2) the patient refused surgery, including clipping or coiling ($n = 8$); (2) the patients were treated without 72 h ($n = 15$); (4) there was a diagnosis of community-acquired pneumonia ($n = 5$). A cohort of 253 patients with aSAH was established and divided into a HAP group ($n = 64$) and a non-HAP group ($n = 189$). The HAP group's inclusion criteria were as similar to the literature (14), which was as follows: (1) new or progressive and persistent infiltrates; (2) body temperature of $>38.3°C$ or leukocytes counts $<4 \times 10^9$/L or $>12 \times 10^9$/L; (3) at least two of the following signs: purulent sputum, cough, dyspnea, declining oxygen saturation, increased oxygen requirement, or need for respiratory assistance.

Data

Clinical characteristics and laboratory tests are displayed in Table 1. The variables were as follows: (1) demographics; (2) comorbidities (i.e., hypertension, diabetes mellitus, hyperlipidemia), and history of smoking and drinking; (3) clinical scores [Glasgow coma scale (GCS), Hunt-Hess score, WFNS; modified Fisher grade]; (4) aneurysm location and occurrence of intracerebral hemorrhage and intraventricular hemorrhage; (5) choice of treatment including coiling or clipping; (6) laboratory tests (peripheral venous blood samples): blood glucose (BG); red blood cell (RBC); hematocrit; hemoglobin, platelets, white blood cell (WBC), neutrophils; monocytes, NLR, platelet to lymphocyte ratio, lymphocyte-to-monocyte ratio; platelet-to-WBC ratio, systemic inflammation response index (SIRI), red blood cell distribution coefficient of variation and red blood cell distribution width-standard deviation (RDW-SD). All clinical characteristics and laboratory tests were collected within 12 h of admission.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 (IBM Inc, Chicago, IL). Continuous variables were expressed as mean

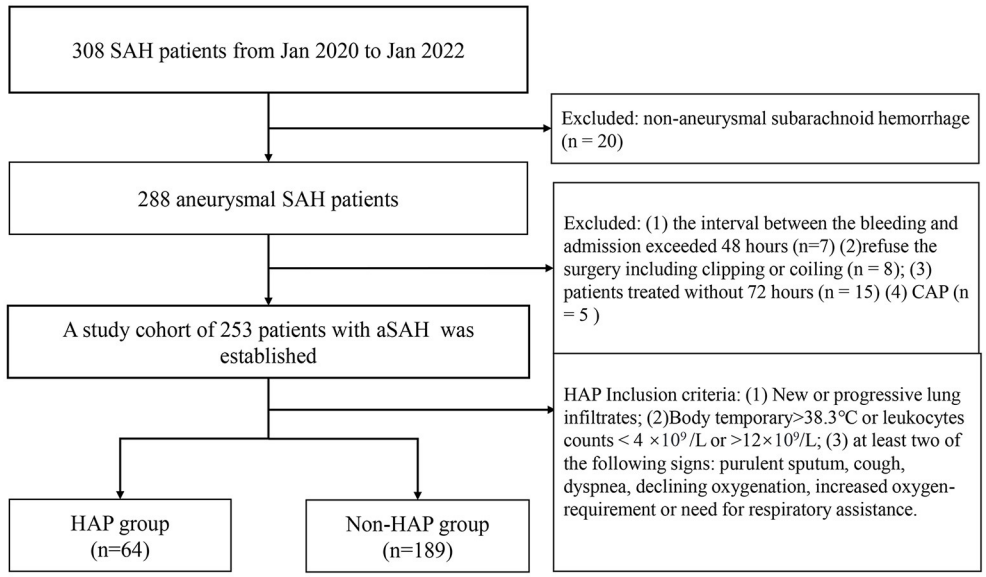

FIGURE 1
The flow chart of patient selection. SAH, subarachnoid hemorrhage; CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia.

± SD. Categorical variables were expressed as frequencies (percentages). The Kolmogorov–Smirnov test was performed to determine whether the parameter dataset was normally distributed. A univariate logistic analysis was used for all variables. Significant parameters were then entered into a multivariate logistic regression using the stepwise forward method to identify the independent risk factors. A logistic model (Model-Logit) was established based on the independent risk factors. We used risk factor categories to develop a new model (Model-Cat). Receiver operating characteristic (ROC) curves were generated to calculate significant variables of areas under the curve (AUCs) and cutoffs. The Delong test was performed to compare the AUCs. Based on the literature (15), predictive scores and corresponding risk estimate were calculated. Differences where $p < 0.05$ were considered statistically significant.

Results

Patient demographics

We included 253 patients with aSAH. Of these, 64 patients developed HAP, with an incidence of 25.30%. In the HAP group, 64 patients included 38 females (59.38%) and 26 males (40.62%) with a mean age of 59.59 (range 44–76 years). In the non-HAP group, 189 patients included 129 females and 60 males with a mean age of 55.27 (range 28–77 years). Demographics are displayed in Table 1.

Predictive factors for HAP

The results of the calculation and univariate analysis are shown in Table 1. The distribution of the significant variables is shown in Figure 2. The univariate logistic regression showed that, compared to the non-HAP group, the HAP group had significantly greater age (59.59 vs. 55.27, $p = 0.001$), BG (9.12 vs. 7.17 mmol/L, $p < 0.001$), WBC (15.82 vs. 10.49, $p < 0.001$), neutrophils (11.87 vs. 8.80, $p < 0.001$), monocytes (0.73 vs. 0.54, $p < 0.001$), NLR (16.17 vs. 10.27, $p < 0.001$), SIRI (12.58 vs. 5.64, $p < 0.001$), and RDW-SD (43.70 vs. 42.11, $p = 0.004$). Diabetes mellitus ($p < 0.001$), Hunt-Hess score ≥ III ($p < 0.001$), intracerebral hemorrhage ($p < 0.001$), and intraventricular hemorrhage ($p < 0.001$) were significantly associated with HAP. Lower GCS scores (9.69 vs. 14.10, $p < 0.001$), lymphocyte-to-monocyte ratios (1.69 vs. 2.44, $p < 0.001$) and platelet-to-WBC ratios (16.02 vs. 22.29, $p < 0.001$) were found in the HAP group. WFNS ≥ II, Hunt-Hess grade ≥ III, and modified Fisher grade ≥2 were significantly associated with HAP. The thresholds to discriminate the higher risk of HAP with cutoff values of the significant continuous variables with the highest sensitivity and specificity are displayed in Table 1.

Using the stepwise forward method, the multivariate logistic regression results are displayed in Table 2. The age [$p = 0.012$, odds ratio (OR) = 1.059, confidence interval (CI) = 1.013–1.107], BG (>7.22 mmol/L; $p = 0.011$, OR = 2.781, CI = 1.263–6.119), RDW-SD ($p = 0.024$, OR = 1.118, CI = 1.015–1.231), and GCS score ($p < 0.001$,

TABLE 1 Clinical characteristics and univariate analysis of the cohorts.

Variables	HAP group ($n = 64$)	Contrast group ($n = 189$)	p-value	Threshold
Age	59.59 ± 7.84	55.27 ± 9.17	**0.001**	**59.50**
Gender	38 (59.38%)	129 (68.25%)		
Female				
Male	26 (40.62%)	60 (31.75%)	0.195	
Hypertension	33 (51.56%)	83 (43.92%)	0.289	
Hyperlipidemia	11 (17.19 %)	41 (21.69 %)	0.441	
DM	12 (18.75 %)	13 (6.88%)	**0.008**	
Smoking	16 (25.00 %)	44 (23.28%)	0.780	
Drinking	19 (29.69%)	44 (23.28%)	0.306	
GCS score	9.69 ± 4.23	14.10 ± 1.90	**<0.001**	**13.5**
Surgery	18 (28.13%)	62 (32.80%)		
EVT				
Clipping	46 (71.87%)	127 (67.20%)	0.487	
Hunt-Hess score			**<0.001**	
I	7 (10.94%)	106 (56.08%)		
II	6 (9.38%)	35 (18.52%)	0.106	
III	20 (31.25%)	38 (20.11%)	**<0.001**	
IV	19 (29.69%)	9 (4.76%)	**<0.001**	
V	12 (18.75%)	1 (0.53%)	**<0.001**	
WFNS			**<0.001**	
I	12 (18.75%)	132 (69.84%)		
II	10 (15.63%)	30 (15.87%)	**0.006**	
III	4 (6.25%)	6 (3.17%)	**0.005**	
IV	14 (21.88%)	19 (10.05%)	**<0.001**	
V	24 (37.50%)	2 (1.06%)	**<0.001**	
Aneurysm location	61 (95.31%)	179 (94.71%)	0.850	
Anterior circulation				
Posterior circulation	3 (4.69%)	10 (5.29%)		
mFisher grade			**<0.001**	
I	16 (25%)	119 (62.96%)		
II	14 (21.88%)	30 (15.87%)	**0.003**	
III	13 (20.31%)	33 (17.46%)	**0.011**	
IV	21 (32.81%)	7 (3.70%)	**<0.001**	
ICH	30 (46.88%)	30 (15.87%)	**<0.001**	
IVH	37 (57.81%)	43 (22.75%)	**<0.001**	
BG, mmol/L	9.12 ± 2.72	7.17 ± 1.91	**<0.001**	**7.22**
PLT, $*10^9$/L	199.73 ± 70.84	214.02 ± 70.39	0.161	
Hb, g/L	126.94 ± 22.24	127.91 ± 17.03	0.715	
RBC, $*10^{12}$/L	4.73 ± 4.01	4.24 ± 0.49	0.101	
HCT, %	38.34 ± 5.87	38.05 ± 4.45	0.678	
WBC, $*10^9$/L	15.82 ± 18.40	10.49 ± 3.78	**<0.001**	**11.92**
Neutrophil, $*10^9$/L	11.87 ± 4.58	8.80 ± 3.82	**<0.001**	**9.08**
Lymph, $*10^9$/L	0.99 ± 0.56	1.11 ± 0.54	0.107	
Monocyte, $*10^9$/L	0.73 ± 0.42	0.54 ± 0.24	**<0.001**	**0.66**
NLR	16.17 ± 10.41	10.27 ± 8.06	**<0.001**	**17.39**
PLR	265.35 ± 204.67	226.10 ± 123.72	0.068	

(Continued)

TABLE 1 (Continued)

Variables	HAP group ($n = 64$)	Contrast group ($n = 189$)	p-value	Threshold
LMR	1.69 ± 1.12	2.44 ± 1.58	**<0.001**	**1.33**
PWR	16.02 ± 7.88	22.29 ± 9.36	**<0.001**	**15.16**
SIRI	12.58 ± 12.71	5.64 ± 5.81	**<0.001**	**5.52**
RDWCV	13.34 ± 1.95	12.89 ± 1.36	0.052	
RDWSD, fl	43.70 ± 3.91	42.11 ± 3.53	**0.004**	**43.05**

DM, diabetes mellitus; GCS, Glasgow coma scale; EVT, endovascular therapy; WFNS, world federal neurological scale; mFisher grade, modified Fisher grade; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage; BG, blood glucose; PLT, blood platelet; Hb, hemoglobin; RBC, red blood cell; HCT, hematocrit; WBC, white blood cell; NLR, neutrophil-lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PWR, PLT to WBC ratio, SIRI, systemic inflammation response index; RDW-CV, red blood cell distribution coefficient of variation; RDW-SD, red blood cell distribution width-standard deviation. Variables showing statistical significance ($p < 0.05$) are in bold.

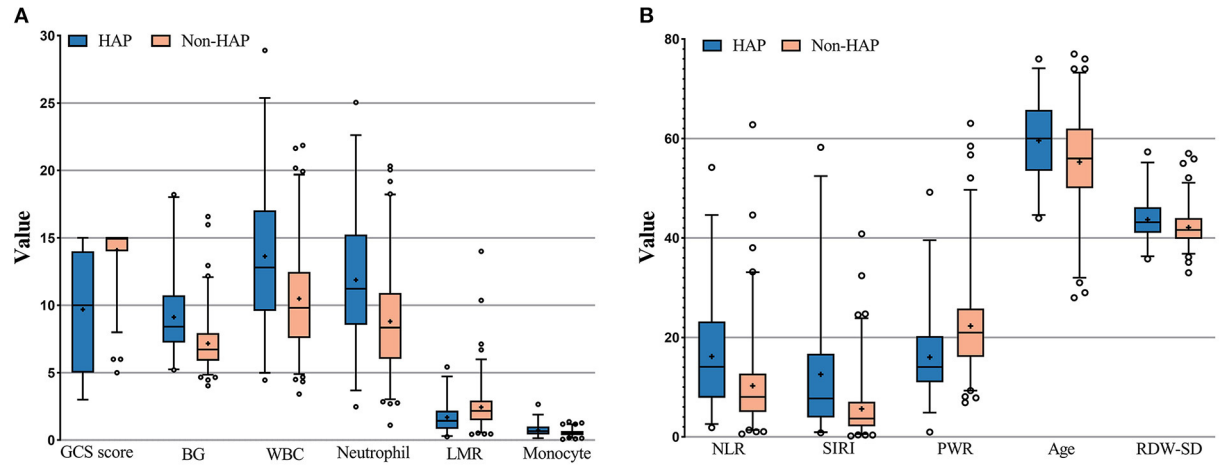

FIGURE 2
(A,B) Measurement of the significant variables in univariate analysis; GCS score, Glasgow coma scale score; LMR, Leukocyte to monocyte ratio; NLF, neutrophil to lymphocyte ratio; SIRI, systemic inflammation response index; PWR, platelet to white blood cell ratio; RDW-SD, red blood cell distribution width standard deviation.

TABLE 2 Results of multivariate logistic regression.

Variables	β value	p-value	OR value	95% CI
Age	0.057	0.012	1.059	1.013–1.107
BG (>7.22 mmol/L)	1.023	0.011	2.781	1.263–6.119
RDW-SD, fl	0.111	0.024	1.118	1.015–1.231
GCS	−0.342	<0.001	0.710	0.633–0.798
Constant	−5.467	0.041	0.004	

OR, odds ratio; CI, confidence interval; RDW-SD: the width of RBC distribution; GCS, Glasgow coma score; OR, odds ratio; CI, confidence interval.

OR = 0.710, CI = 0.633–0.798) were independent risk factors. Based on these independent risk factors, we established the Model-Logit and the Model-Cat (Table 3). Corresponding points and risk estimates are displayed in Table 4.

Model-Logit and Model-Cat

The Model-Logit was as follows: Logit(P) = −5.467 + 0.057 * age + 1.023 * BG (>7.22 mmol/L, yes = 1, no = 0) + 0.111 * RDW-SD−0.342 * GCS. This model was accurate but inconvenient for clinical use. Therefore, we established a Model-Cat (Table 3) whose method is similar to Wilson et al. (15). Based on our samples. The reference values (W_{ij}) are displayed in Table 3. We set the basic risk value ($W_{i\mathrm{REF}}$) of age, BG (>7.22), GCS, and RDW-SD as 44.5, 0, 14, and 40, respectively. When the parameters exceeded the $W_{i\mathrm{REF}}$, the greater points represented higher risks. The distance (D) was calculated based on the equation: $D = \beta_i^* \left(W_{ij} - W_{REF}\right)$. We set the constant ($B$) change of each risk factor for each point in the model. We regarded every increase of 10 years of the age as one point, as follows: $B = 10^* \beta_{age}$, $\mathrm{Points}_i = D_i/B$. Finally, the risk estimate (P) corresponding to the total score was based on the following equation:

TABLE 3 Predictive model using risk factor categories.

Risk factor	Categories	Reference value	W_{ij}-W_{iREF}	*D*	Points
Age	20–29	24.5	−20	−1.14	−2
	30–39	34.5	−10	−0.57	−1
	40–49	$44.5 = W_{1REF}$	0	0	0
	50–59	55.5	10	0.57	1
	60–69	65.5	20	1.14	2
	70–79	75.5	30	1.71	3
BG, mmol/L	<7.22	$0 = W_{2REF}$	0	0	0
	≥7.22	1	1	1.02	2
GCS score	3–8	5.5	−8.5	2.91	5
	9–12	10.5	−3.5	1.20	2
	13–15	$14 = W_{3REF}$	0	0	0
RDW-SD, fl	<35	34	−6	−0.67	−1
	≥35; <45	$40 = W_{4REF}$	0	0	0
	≥45; <55	50	10	1.11	2
	≥55	60	20	2.22	4

BG, blood glucose; GCS score, Glasgow coma scale score; RDW-SD, red blood cell distribution width standard deviation; W_{ij}, reference value; W_{REF}, the basic risk value; D, distance, $D = \beta^{*}(W_{ij} - W_{iREF})$; $Points_i = D_i/B$.

$$P = \frac{1}{1 + \exp\left(-\sum_{i=0}^{p} \beta_i \chi_i\right)}; \sum_{i=0}^{p} \beta_i \chi_i = \beta_{constant} + \beta^{*}_{Age} W_{1REF} + \beta^{*}_{BG} W_{2REF} + \beta^{*}_{GCS} W_{3REF} + \beta^{*}_{4} W_{4REF} + B^{*} Total\ score = 0.57^{*} Total\ score - 3.2785.$$

Total scores ranged from −3 to 14 points. The total points and risk estimates are displayed in Table 4.

To verify the model of risk factor categories, we generated ROC curves in both models. In the Model-Logit, the AUC of the Model-Logit, GCS, age, BG (>7.22 mmol/L), and RDW-SD were 0.865, 0.819, 0.634, 0.698, and 0.625, respectively (Figure 3). The Delong test showed that the AUC of the Model-Logit was significantly higher than the GCS ($p = 0.0386$), age ($p < 0.001$), BG (>7.22 mmol/L; $p < 0.001$), and RDW-SD ($p < 0.001$). In the Model-Cat, the AUCs for GCS, age, BG, and RDW-SD were 0.850, 0.760, 0.700, 0.641, and 0.564, respectively (Figure 4A). The Delong test was also performed to compare the ROC curves between the models. The difference in areas was 0.015; however, the AUC of the Model-Logit was insignificantly higher than that of the Model-Cat ($p = 0.157$). This finding suggests that the Model-Cat is convenient, and the accuracy is close to Model-Logit. Cutoff values of the Model-Logit and Model-Cat were −0.849 and 4.5 points, respectively. Therefore, we considered scores of −3 to 4 as the low-risk group and 5–14 as the high-risk group. Low- and high-risk cohorts are represented in Figure 4B.

TABLE 4 Estimate of risk corresponding to total scores.

Total scores	Estimate of risk	Total scores	Estimate of risk
−3	0.68%	6	53.53%
−2	1.19%	7	67.07%
−1	2.09%	8	78.27%
0	3.63%	9	86.43%
1	6.25%	10	91.85%
2	10.54%	11	95.22%
3	17.24%	12	97.24%
4	26.92%	13	98.42%
5	39.45%	14	99.10%

Discussion

Aneurysmal subarachnoid hemorrhage (aSAH) accounts for ∼5% of strokes (16). Despite substantial advancements in the care of aSAH, the mortality rates are 32%−67%, and one-third become dependent on care (2). About one-third of patients with SAH suffer from systemic infections (mainly pneumonia), which can lead to additional mortality after SAH (3, 5). Cerebral hypoxia due to disturbed cerebral circulation generates exogenous materials that cause early brain injury (2, 17). For these reasons, preventing hypoxia is critical. Pulmonary complications damage air exchange and worsen hypoxia, aggravating brain injury (1, 2). Therefore, evaluating the possibility of developing pneumonia during hospitalizations

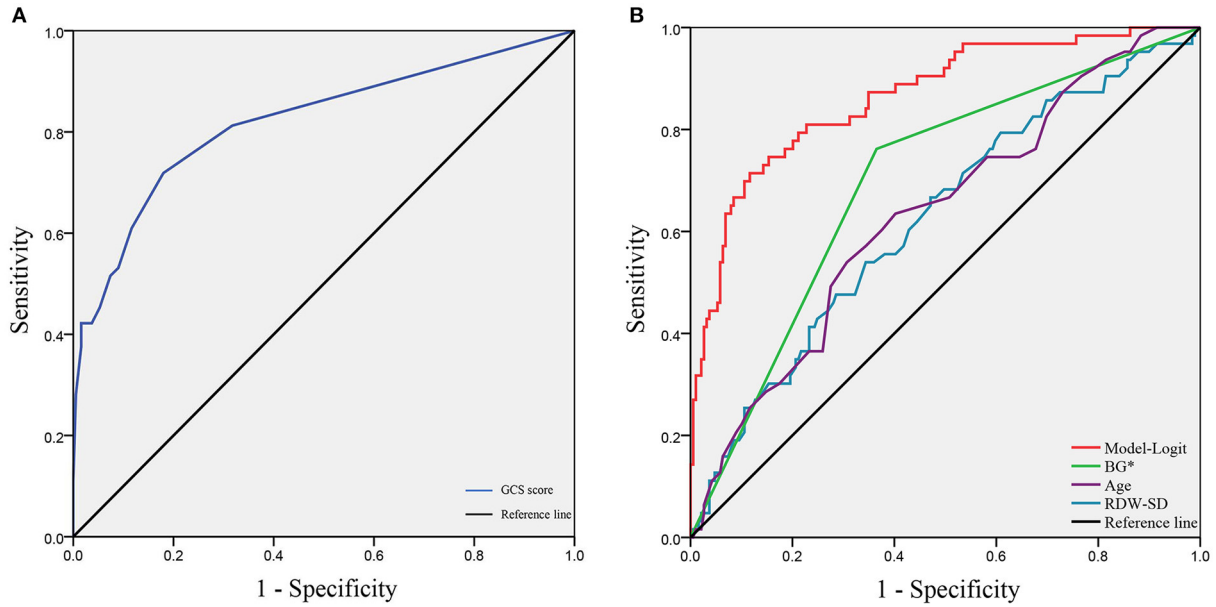

FIGURE 3
ROC analysis of the Model-Logit and independent risk factors. **(A)** GCS score as a protective role with the AUC of 0.819; **(B)** AUCs of the Model-Logit, BG*, age, and RDW-SD are 0.865, 0.698, 0.634, and 0.625, respectively. Model-Logit, logistic model; GCS score, Glasgow coma scale score; BG*, blood glucose (>7.22 mmol/L); RDW-SD, red blood cell width distribution standard deviation.

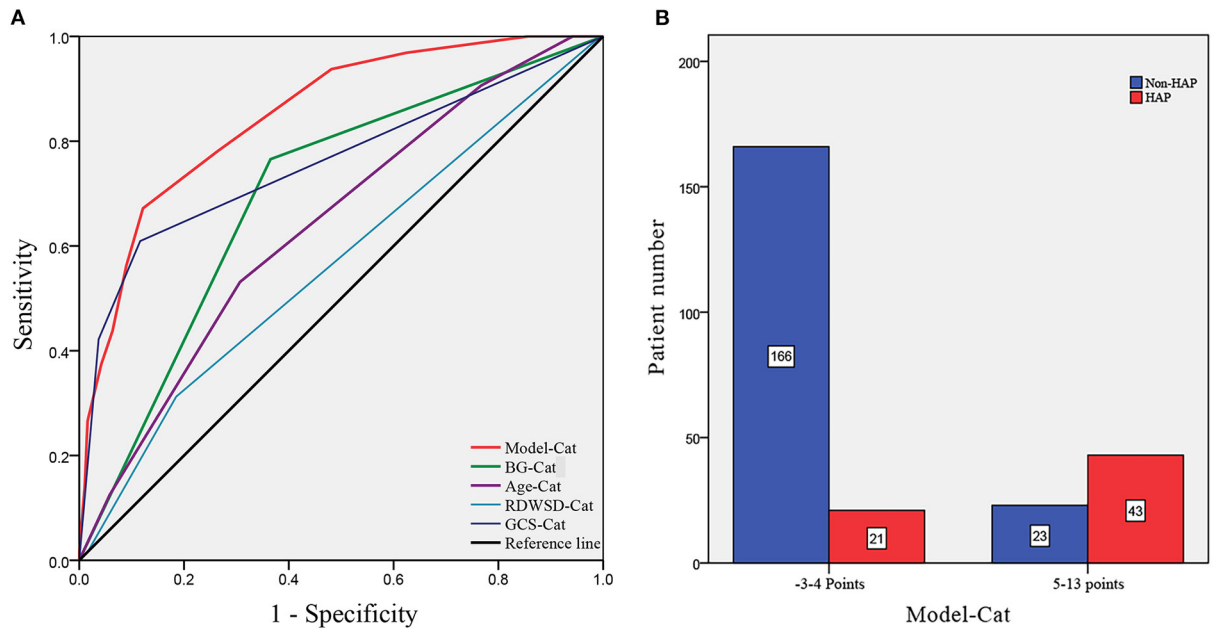

FIGURE 4
ROC analysis of the Model-Cat and risk level classification. **(A)** AUCs of the Model-Cat, BG-Cat, Age-Cat, RDWSD-Cat, and GCS-Cat were 0.850, 0.700, 0.641, and 0.564, and 0.760, respectively. **(B)** Patient numbers are classified as low-risk level (−3 to 4 points) and high-risk level (5–14 points). Model-Cat, predictive model using risk factor category; Glu-Cat, blood glucose (>7.22 mmol/L) category; Age-Cat, age category; RDWSD-Cat, red blood cell distribution standard deviation category; GCS-Cat, Glasgow coma scale score category.

in the early stage and subsequently avoiding potential risk factors is desirable to prevent HAP and improve outcomes in aSAH patients (4).

Hospital-acquired pneumonia in aSAH requires attention. Kumar et al. (18) demonstrated that individuals with HAP had worse long-term outcomes. Khanzadeh et al. (19) showed NLR could be recommended as a biomarker for predicting infection, particularly pneumonia, in stroke patients. Some studies returned inconsistent results and identified independent risk factors, including weekend admission, Hunt-Hess grade III, external ventricular drain, male sex, use of mannitol, enteral feeding, WFNS score, and neutrophil count (4, 20). They did not apply a specific value to discriminate against high risk. Age, BG, RDW-SD, and GCS were independent risk factors in our study. A Model-Cat was established, and the AUC was close to that of the Model-Logit (0.850 vs. 0.865, Delong test, $p = 0.157$), which could aid practical evaluation.

Advanced age is associated with more risk of HAP in aSAH patients. HAP cohorts had a mean age of 59.59 years old, with a threshold of 59.50 years old. Wang et al. and Ding et al. stressed the significance of age, and their mean value was higher than ours (61, 59.79 vs. 59.50). The optimal threshold was age c60, and the patients with aSAH were at high risk. The World Health Organization defines older people as those over 60. Thus, in clinical use, older people (The optimal threshold w60) with aSAH had a higher risk of HAP.

Blood glucose (>7.22 mmol/L) is a two-category variable applied to the risk threshold with a predictive value. High glucose levels are frequently associated with vasospasm, secondary ischemia, and poor outcomes (2, 21, 22). Hyperglycemia might be expected in aSAH patients due to the transient stress reaction and an acute metabolic response (21). Zhang et al. (23) found that the BG of SAH patients with poor outcomes had a mean value of 7.34 mmol/L, which exceeded the threshold of 7.22 in our study. Eagles et al. (13) identified an optimal BG target in aSAH patients (<9.2 mmol/L), which is close to the BG value (9.12 mmol/L) in our HAP cohort. Abulhasan et al. (24) analyzed 419 patients with aSAH and found that BG (>10 mmol/L) increased the risk of pneumonia. In our study, the risk of HAP would increase 2.781-fold when the admission BG exceeded 7.22 mmol/L.

Low GCS is a common predictor of poor outcomes in intracranial hemorrhage; a pulmonary infection might be the explanation. In our study, the mean value of GCS in the HAP group was lower significantly than in the non-HAP group (9.69 vs. 14.10). Consistent with our results, several studies also found that low GCS was associated with a higher risk of developing pneumonia in aSAH patients (11). Wang et al. (4) found that HAP patients had lower GCS scores than the threshold of GCS in our study (12 < 13.5). Dunn et al. (25) reported an independent association between GCS and dysphagia. Dysphagia could increase the risk of aspiration pneumonia and lung infections. The GCS reflects the extent of the brain injury, and the subsequent impaired cardiopulmonary function and systematic inflammation could produce worse outcomes (4). Chaudhry et al. (3) also stressed that immunodepression is probably the most crucial mechanism leading to pneumonia infections after aSAH. The study of Faura et al. (16) highlighted that stroke generated powerful inflammatory cascades and the peripheral immune system immunosuppression, which could enhance the risk of infection.

Red blood cell distribution width-SD refers to the degree of variation in the volume of red blood corpuscle in circulating plasma (12). Several lines of evidence suggested that RDW-SD was significantly associated with systemic inflammatory responses (26, 27). Nakamura et al. (27) reported that substantial destroyed RBCs follow activated inflammatory responses, which promote hematopoiesis and accelerate the production of immature RBCs. Thus, increased RDW-SD could serve as a proxy for an inflammatory state. An aneurysm rupture would cause brain injury and cause a systematic inflammatory response. Peripheral immunosuppression further aggravates the risk of infection (16). Furthermore, there is no specific value to identify the risk of HAP. In our study, higher RDW-SD could increase the risk of HAP in aSAH patients, with a threshold of 43.05.

Even though any single markers presented good performance in predicting HAP, they were only highlighted by their significance and applied thresholds. Numerous factors contributed to the results. Predictive models could aid these evaluations. Model-Logit was established; it is accurate but inconvenient for clinical use. The Model-Cat using the risk factor categories was superior. The AUC of the Model-Cat was insignificantly lower than that of the Model-Logit (0.850 vs. 0.865, Delong test, $p = 0.157$). Furthermore, the AUCs of models exceeded any single marker. The risk estimate corresponding to the total point could be used in future studies.

Previous studies paid scarce attention to valid predictive models. Wang et al. proposed a model that included simplified scores of WFNS, neutrophils, RBC transfusion, and tracheostomy (4). It performed well with an AUC of 0.808 and a cutoff of 0.2696 to identify high-risk patients. Our Model-Cat presented a higher AUC (0.850 vs. 0.808) and provided risk factor categories to identify individualized risks. The optimal cutoff of the Model-Cat was 4.5, and patients could be divided into low-risk (−3 to 4 points) and high-risk cohorts (5 to 14 points). Effective prevention should be implemented in high-risk HAP patients with aSAH.

There were several limitations in this study. First, we only considered aSAH in a single institute from 2020 to 2022. The limited sample size might have decreased the accuracy of our findings. Second, our study did not consider tracheotomy and mechanical ventilation. We aimed to test the admission state to evaluate the risk of HAP; these factors may cause selection bias. Third, drug usage records were not recorded. Mannitol, crystalloid, nimodipine, anticonvulsant, and proton pump inhibitors might influence the development of HAP. Fourth, some laboratory parameters were not included (e.g.,

procalcitonin, IL-10, and C-reactive protein). Fifth, we did not involve parameters correlated with the COVID-19, even though the COVID-19 could enhance the possibilities of the aneurysm rupture (28). Finally, some clinical manifestations were not included: dysphagia, dysarthria, and hearing failure (7, 8). In future studies, more cases should be gathered at several centers to identify other independent risk factors and increase the predictive model's accuracy.

Conclusions

In this retrospective study, age, BG (>7.22 mmol/L), GCS, and RDW-SD were independent risk factors for HAP in aSAH patients. The Model-Cat was close to the Model-Logit but more convenient for practical evaluation. The aSAH patients with total points from 5 to 14 had a high-risk HAP level. They require attention during treatment.

Data availability statement

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

Ethics statement

This study was reviewed and approved by institutional ethics committee at Tongji Hospital. Written informed consent was obtained from all participants or their legal guardians/next of kin for their participation in this study.

Author contributions

S-QH and J-NH: conceptualized the study, wrote the manuscript, collected, and analyzed data. R-DC: revised the draft paper. J-SY: supervision. 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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Incidence of intra-procedural complications according to the timing of endovascular treatment in ruptured intracranial aneurysms

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Background: Although endovascular treatment of ruptured intracranial aneurysms is well-established, some critical issues have not yet been clarified, such as the effects of timing on safety and effectiveness of the procedure. The aim of our study was to analyze the incidence of intra-procedural complications according to the timing of treatment, as they can affect morbidity and mortality.

Materials and methods: We retrospectively analyzed all patients who underwent endovascular treatment for ruptured intracranial aneurysms at three high flow center. For all patients, imaging and clinical data, aneurysm's type, mean dimension and different treatment techniques were analyzed. Intra-procedural complications were defined as thrombus formation at the aneurysm's neck, thromboembolic events, and rupture of the aneurysm. Patients were divided into three groups according to time between subarachnoid hemorrhage and treatment (<12 h hyper-early, 12–36 h early, and >36 h delayed).

Results: The final study population included 215 patients. In total, 84 patients (39%) underwent hyper-early, 104 (48%) early, and 27 (13%) delayed endovascular treatment. Overall, 69% of the patients were treated with simple coiling, 23% with balloon-assisted coiling, 1% with stent-assisted coiling, 3% with a flow-diverter stent, 3% with an intrasaccular flow disruptor device, and 0.5% with parent vessel occlusion. Delayed endovascular treatment was associated with an increased risk of total intra-procedural complications compared to both hyper-early ($p = 0.009$) and early ($p = 0.004$) treatments with a rate of complications of 56% (vs. 29% in hyper-early and 26% in early treated group—$p = 0.011$ and $p = 0.008$). The delayed treatment group showed a higher rate of thrombus formation and thromboembolic events.

The increased risk of total intra-procedural complications in delayed treatment was confirmed, also considering only the patients treated with simple coiling and balloon-assisted coiling ($p = 0.005$ and $p = 0.003$, respectively, compared to hyper-early and early group) with a rate of complications of 62% (vs. 28% in hyper-early and 26% in early treatments—$p = 0.007$ and $p = 0.003$). Also in this subpopulation, delayed treated patients showed a higher incidence of thrombus formation and thromboembolic events.

Conclusions: Endovascular treatment of ruptured intracranial aneurysms more than 36 h after SAH seems to be associated with a higher risk of intra-procedural complications, especially thrombotic and thromboembolic events.

KEYWORDS

ruptured intracranial aneurysm, endovascular treatment, intra-procedural complications, timing of endovascular treatment, subarachnoid hemorrhage

Introduction

Subarachnoid hemorrhage (SAH) due to aneurysmal rupture is associated with important mortality and morbidity (1, 2). Ruptured intracranial aneurysms may be treated surgically or endovascularly. The multicenter randomized controlled International Subarachnoid Aneurysm Trial (ISTAT) compared the surgical clipping and endovascular simple coiling of ruptured intracranial aneurysms (1, 2). The ISTAT study provided important information regarding the indications of the different types of treatment and their clinical outcomes, concluding that patients treated endovascularly had a better clinical outcome at 1 year and a similar clinical outcome at 5 years (2). Although the endovascular treatment for ruptured intracranial aneurysms is well-established and widely used, the effect of the treatment's timing on its safety is poorly understood. In 2012, the American Heart Association (AHA) together with the American Stroke Association (ASA) recommended the treatment of ruptured aneurysms as early as feasible to reduce the risk of rebleeding (3). In 2013, the European Stroke Organization underlined that the treatment should be aimed at least within 72 h after onset of first symptoms (4). Only few studies have focused on the best timing of treatment after SAH and most of them included only surgical clipping or both surgical and endovascular treatments (5–16). The definition of hyper-early, early, and delayed treatment varies widely in the different studies and their results are contradictory. By comparing patients treated within 48 h and patients treated between 48 h and 30 days after symptom onset, Baltsavias et al. (12) showed that the timing of endovascular treatment did not influence the periprocedural morbidity and the clinical outcome at 6 months. Philips et al. (13) demonstrated that in their mixed surgical and endovascular series, the patients treated within 24 h after symptom onset had a better clinical outcome at 6 months. These data were confirmed by Consoli et al. (14), who demonstrated that hyper-early endovascular treatment within 12 h after SAH is not associated with a lower morbidity or a better clinical outcome with respect to treatment after 12 h. Recently, Buscot et al. (15) and Wu et al. (16) showed that best clinical outcomes were achieved treating the patients at ∼12.5 h.

Despite these studies, the effects of timing of endovascular procedure, not only on the medium-term clinical outcome, but also on intra-procedural complications, which may affect morbidity and mortality, in patients with ruptured intracranial aneurysms, are still unclear. Thus, the aim of this multicenter study was to analyze the incidence of intra-procedural complications according to the timing of endovascular treatment in a large series of patients who underwent endovascular treatment for ruptured intracranial aneurysms.

Materials and methods

Study design and patient population

We retrospectively analyzed 226 patients treated endovascularly for ruptured intracranial aneurysms at three high flow centers in 3 consecutive years. Patients were not randomized.

Clinical and imaging data

At admission, all patients underwent clinical evaluation, brain computed tomography (CT), and a CT angiography. Then, each patient underwent a digital subtraction angiography (DSA) on a flat panel unit with 3D rotational acquisition. Each case was evaluated by the neurosurgeon and the interventional neuroradiologist to decide the choice of treatment: endovascular

treatment was preferred except in big hematomas with mass effect and in case of arterial branches originating from the aneurysm's sac. The timing of endovascular treatment was left up to the discretion of treatment teams. Imaging and clinical data of patients treated endovascularly were retrospectively analyzed by three experienced interventional neuroradiologists (with more than 8 years of clinical practice; C.G., F.B., and V.D.R.) using the modified Fisher's and Hunt and Hess scale. For each patient, aneurysm's location and type (saccular with narrow or wide neck, dissecting, and blister), mean aneurysm's dimension, and different endovascular treatment techniques (simple coiling, balloon-assisted coiling, stent-assisted coiling, placement of flow-diverter stents, or intrasaccular flow-disruptor and parent vessel occlusion) were considered. Intra-procedural complications were defined as thrombus formation at the aneurysm's neck, thromboembolic events, and rupture of the aneurysm. For each patient, general risk factors such as hypertension, diabetes mellitus, dyslipidemia, anticoagulation, and antiplatelet therapy before SAH were considered. Patients were divided into three groups according to time between SAH and treatment: <12 h = hyper-early, 12–36 h = early, and >36 h = delayed. The interventional neuroradiologists were blinded regarding the timing of endovascular treatment, while analyzing the clinical and imaging data.

Sample size calculation

The primary objective of our study was to investigate the incidence of intra-procedural complications according to the timing of treatment, as they can affect morbidity and mortality in patients with SAH. Considering three groups (<12 h = hyper-early, 12–36 h = early, and >36 h = delayed), an alpha error of 0.05, a power of 0.9, and an effect size of 0.25, we calculated that a minimum sample size of 207 patients with SAH is required (Gpower, Heinrich-Heine-Universität Düsseldorf).

Statistical analysis

Demographic, clinical, imaging, and angiographic data were analyzed using SPSS software (IBM SPSS Statistics for Windows, version 26.0, IBM Corporation, Armonk, NY, USA, RRID:SCR_002865). Continuous variables were presented as median and interquartile range (IQR), depending on the distribution of data. Categorical variables were presented as counts and percentages. Demographic and clinical parameters were tested for normality using the Kolmogorov–Smirnov and Shapiro–Wilk tests. When normally distributed, a two-way ANOVA was used to compare, simultaneously, the different variables between the three treatment groups; otherwise, when not-normally distributed, the variables were compared by the Kruskal–Wallis test for the independent samples. Chi-square test was used to perform the statistical analysis in global population and within the three different treatment groups. The odd ratio (OR) was calculated using the logistic regression analysis.

Also, multivariate analysis with logistic regression was performed within the different treatment groups. To select the variables for the multivariate analysis, the total study population was divided into two groups according to the presence or absence of intra-procedural complications and univariate analysis was conducted to identify the association between baseline characteristics and intra-procedural complications. Qualitative variables were analyzed by chi-square test. Quantitative variables, when normally distributed, were analyzed by the two-tailed Student's *t*-test; otherwise, when not normally distributed, no-parametric Mann–Whitney test was performed.

The tests were considered statistically significant when $p < 0.05$.

Results

We retrospectively analyzed 226 consecutive patients treated endovascularly for ruptured intracranial aneurysms; 11 patients were excluded because they were treated more than 4 days after SAH. The final study population included 215 patients with 216 aneurysms (74 men and 141 women; mean age: 58.2 ± 12.5 years, range: 29–91 years). Clinical and imaging data at admission are summarized in Table 1. All patients were treated as soon as possible after admission: 84 patients (39%) were treated in the first 12 h, 104 patients (48%) between 12 and 36 h, and 27 patients (13%) more than 36 h after aneurysm's rupture.

Computed tomography scan at admission was positive for SAH in 214 patients. In one patient, SAH was diagnosed with lumbar puncture. In 192 patients (89%), the aneurysm was located in the anterior circulation and in 23 (11%), the aneurysm was located in the posterior circulation. The ruptured aneurysm was saccular with narrow neck in 111 cases (52%), saccular with wide neck in 78 cases (36%), dissecting in 20 cases (9%), and blister in seven cases (3%).

The three treatment groups did not differ significantly for age distribution, risk factors, and Fisher's grade (Table 1). Hunt and Hess grade 1 was more frequent in the delayed than in the hyper-early treated group (10 of 27 patients −37% vs, 13 of 84 patients −16%; $p = 0.049$). Blisters aneurysms were more frequent in the delayed than in hyper-early and early groups (4 of 27 patients −15% vs. 0 of 84 patients −0% and 3 of 104 patients 3%, respectively; $p = 0.01$; Figure 1A). Pre-treatment rebleeding was observed in 12 patients (5.6%): six of 84 patients (7.1%), four of 104 patients (3.8%), and two of 27 patients (7.4%)

TABLE 1 Demographic and clinical parameters in hyper-early, early, and delayed treatment groups.

		<12 h	12–36 h	>36 h	Tot	*p*-value
Patients, *n*° (%)		84 (39)	104 (48)	27 (13)	215 (100)	n.s
Age, median (IQR), year		55 (48–64)	60 (50–69)	56 (45–70)	58 (49–57)	n.s.
Sex M/F, *n*° (%)		28/56 (33/67)	31/73 (70/30)	15/12 (44/56)	113/102 (52/48)	n.s.
Treatment time from SAH, mean ± std dev, h		7.2 ± 2.4	19.01 ± 5.7	59.8 ± 17.25	19.6 ± 17.9	n.s.
Hunt Hess, *n*° (%)	1	13 (15.5)	31 (29.8)	10 (37.0)	54 (25.1)	$p < 0.05$
	2	32 (38.1)	38 (36.5)	11 (40.8)	81 (37.7)	n.s.
	3	17 (20.2)	18 (17.3)	3 (11.1)	38 (17.7)	n.s.
	4	17 (20.2)	14 (13.5)	3 (11.1)	34 (15.8)	n.s.
	5	5 (6)	3 (2.9)	0 (0)	8 (3.7)	n.s.
Modified Fisher, *n*° (%)	0	0 (0)	0 (0)	1 (3.7)	1 (0.5)	n.s.
	1	11 (13.1)	25 (24.0)	11 (40.7)	47 (21.9)	n.s.
	2	29 (34.5)	37 (35.6)	5 (18.5)	71 (33.0)	n.s.
	3	18 (21.4)	16 (15.4)	5 (18.5)	39 (18.1)	n.s.
	4	26 (30.9)	26 (25.0)	5 (18.5)	57 (26.5)	n.s.
Rebleeding before treatment, *n*° (%)		6 (7.1)	4 (3.8)	2 (7.4)	12 (5.6)	n.s.
Location, *n*° (%)	ICA	14 (16.6)	24 (22.8)	6 (22.2)	44 (20.3)	n.s.
	PcomA	12 (14.3)	11 (10.5)	4 (14.8)	27 (12.5)	n.s.
	MCA	12 (14.3)	10 (9.5)	4 (14.8)	26 (12.0)	n.s.
	ACA	16 (19.0)	10 (9.5)	0 (0)	26 (12.0)	n.s.
	AcomA	24 (28.6)	36 (34.3)	10 (37.1)	70 (32.4)	n.s.
	VA	0 (0)	4 (3.8)	0 (0)	4 (1.9)	n.s.
	PICA	1 (1.2)	7 (6.7)	3 (11.1)	11 (5.1)	n.s.
	BA	4 (4.8)	2 (1.9)	0 (0)	6 (2.8)	n.s.
	SCA	0 (0)	1 (1)	0 (0)	1 (0.5)	n.s.
	PCA	1 (1.2)	0 (0)	0 (0)	1 (0.5)	n.s.
Dimension, median (IQR) (mm)		5.25 (3.97–7.15)	4.7 (3.7–6.7)	4.0 (3.3–5.3)	4.8 (3.7–6.5)	n.s.
Type, *n*° (%)	Saccular with narrow neck	42 (50)	58 (55.2)	11 (40.8)	111 (51.4)	n.s.
	Saccular with wide neck	37 (44.0)	32 (30.5)	9 (33.3)	78 (36.1)	n.s.
	Blister	0 (0)	3 (2.9)	4 (14.8)	7 (3.2)	$p \leq 0.01$
	Dissecting	5 (6)	12 (11.4)	3 (11.1)	20 (9.3)	n.s.
All complication, *n*° (%)		24 (28.6)	27 (26.0)	15 (55.6)	66 (30.7)	$p \leq 0.01$
Rupture, *n*° (%)		8 (9.5)	5 (4.8)	4 (14.8)	17 (7.9)	n.s.
Thromboembolic events, *n*° (%)		18 (21.4)	26 (25.0)	11 (40.7)	55 (25.6)	$p < 0.05$
Event resolution, *n*° (%)		10 (41.7)	15 (55.6)	8 (53.3)	33 (50)	n.s.
Secondary lesion, *n*° (%)		8 (9.5)	12 (11.5)	4 (14.8)	24 (11.2)	n.s.

(Continued)

TABLE 1 (Continued)

		<12 h	12–36 h	>36 h	Tot	*p*-value
Endovascular treatment, *n*° (%)	Simple coiling	56 (66.6)	78 (74.3)	15 (55.6)	149 (69.0)	n.s.
	Balloon-assisted coiling	26 (31.0)	18 (17.1)	6 (22.2)	50 (23.1)	n.s.
	Stent and coiling	1 (1.2)	0 (0)	2 (7.4)	3 (1.4)	n.s.
	Flow-diverter stent	0 (0)	5 (4.8)	1 (3.7)	6 (2.8)	n.s.
	WEB	1 (1.2)	3 (2.8)	3 (11.1)	7 (3.2)	$p < 0.05$
	Parent vessel occlusion	0 (0)	1 (1.0)	0 (0)	1 (0.5)	n.s.
Anticoagulation therapy during treatment, *n*° (%)		55 (65.5)	70 (67.3)	19 (70.3)	144 (67.0)	n.s.
	i.v. bolus	26 (31.0)	45 (43.3)	11 (40.7)	82 (38.1)	n.s.
	Infusion through catheter	8 (9.5)	13 (12.5)	5 (18.5)	26 (12.1)	n.s.
	Infusion through microcatheter	21 (25.0)	12 (11.5)	3 (11.1)	36 (16.7)	n.s.
Antiplatelet therapy during treatment, *n*° (%)		12 (14.3)	13 (12.5)	7 (25.9)	32 (14.9)	n.s.
Previous anticoagulation or antiplatelet, *n*° (%)		9 (10.7)	20 (19.2)	5 (18.5)	34 (15.8)	n.s.
Risk factors, *n*° (%)	Hypertension	41 (48.8)	54 (51.9)	17 (63.0)	112 (52.1)	n.s.
	Diabetes mellitus	5 (6.0)	14 (13.5)	4 (14.8)	23 (10.7)	n.s
	Dyslipidemia	7 (8.3)	22 (21.2)	7 (25.9)	36 (16.7)	n.s

p-value comparing hyper-early, early, and delayed treatment groups.
n.s., not significant; ICA, internal carotid artery; PcomA, posterior communicating artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; AcomA, anterior communicating artery; VA, vertebral artery; PICA, posterior inferior cerebellar artery; BA, basilar artery; SCA, superior cerebellar artery; PCA, posterior cerebral artery.

in the hyper-early, early, and delayed groups, respectively (p = n.s.).

In total, 149 of 215 patients (69%) were treated with simple coiling, 50 patients (23%) with balloon-assisted coiling, three patients (1%) with stent-assisted coiling, six patients (3%) with the deployment of a flow-diverter stent, seven patients (3%) with an intrasaccular flow disruptor device (Woven EndoBridge—WEB) and one patients (0.5%) with parent vessel occlusion. The WEB device was more frequently used in the delayed group compared to the hyper-early group (3 of 27 patients −11% vs. 1 of 84 patients −1.2%; $p = 0.048$; Figure 1B). The three treatment groups did not differ significantly either for the others treatment techniques or for the anticoagulation or antiplatelet therapy during or previous endovascular treatment (Table 1). Activated clotting time (ACT) was not tested during the intervention.

Patients treated after 36 h showed a significantly higher rate of total intra-procedural complications (15 of 27 patients −56%) compared to both hyper-early (24 of 84 patients −29%) and early (27 of 104 patients −26%) groups ($p = 0.011$ and $p = 0.008$, respectively; Figure 2A). Accordingly, delayed treatment was associated with an increased risk of total complications with respect to both hyper-early and early treatment groups (OR: 3.315, 95% CI: 1.351–8.137, $p = 0.009$, and OR: 3.565; 95% CI: 1.484–8.565, $p = 0.004$, respectively). More in detail, the delayed treatment group showed a higher rate of thrombus formation and thromboembolic events (12 of 27 patients −44%), compared to hyper-early (17 of 84 patients −21%; $p = 0.037$) and early (26 of 104 patients −25%; p = n.s.) treated patients (Figure 2B). The three treatment groups did not differ significantly for the incidence of aneurysm's rupture during endovascular treatment: seven of 84 patients −10%; five of 104 patients −5%; four of 27 patients −15%, in the hyper-early, early, and delayed treatment groups, respectively (p = n.s.; Figure 2C). The complication was resolved in 33 of 66 cases (50%) and only 24 of 215 patients (11%) presented a secondary lesion related to the event.

Univariate logistic regression analysis comparing patients with intra-procedural complications and patients with no complications revealed that treatment time from SAH (χ^2; $p = 0.041$), Hunt and Hess grade (χ^2; $p = 0.036$), and heparin during procedure (χ^2; $p = 0.037$) were significantly associated with intra-procedural complications. Variables with moderate to high association, without reaching the significance level, were modified Fisher (χ^2; $p = 0.315$), rebleeding before treatment (χ^2; $p = 0.267$), antiplatelets and/or anticoagulant therapy at home (χ^2; $p = 0.063$), and aneurysm's location (χ^2; $p = 0.207$). Interestingly, multivariate logistic regression analysis, conducted with above-mentioned significant predictors

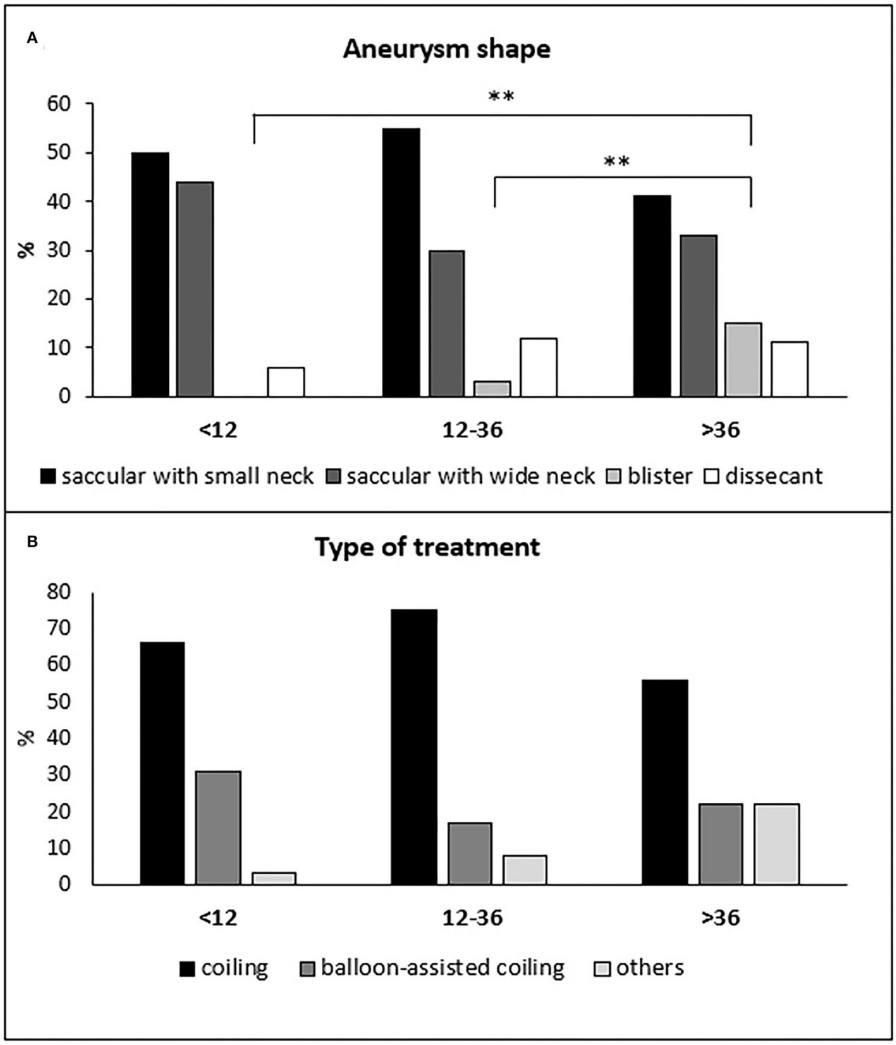

FIGURE 1
Distribution of the different aneurysm shapes **(A)** and types of treatments **(B)** in the hyper-early, early, and delayed treatment groups of patients. **(A)** $^{**}p \leq 0.01$.

and variables with moderate to high association, revealed that, within the three different treatment groups, only treatment time from SAH was an independent predictor factor for aneurysm treatment complications [OR: 1.757, (95% CI: 1.073–2.879); $p = 0.025$; Table 2].

Due to the higher risk of thrombus formation and thromboembolic events associated with stent-assisted coiling, flow-diverter stent, and WEB in the acute phase, we analyzed the subpopulation of 199 patients treated with simple coiling (149 patients) and balloon-assisted coiling (50 patients). There were 82 patients (41%) with hyper-early, 96 patients (48%) with early, and 21 patients (11%) with delayed treatments. Considering only the patients treated with simple coiling and balloon-assisted coiling, we have excluded all patients with blister aneurysms, with no difference in the distribution of the other aneurysm types in the three treatment groups. Also, in this subpopulation of patients, the delayed treatment was associated with a higher rate of total intra-procedural complications (13 of 21 patients −62%) compared to both hyper-early (23 of 82 patients −28%; $p = 0.007$), and early (25 of 96 patients −26%; $p = 0.003$) groups (Figure 3A). Delayed treatment was associated with an increased risk of total complications with respect to both hyper-early and early treated groups (OR: 4.168, 95% CI: 1.528–11.375, $p = 0.005$ and OR: 4.615; 95% CI: 1.712–12.441, $p = 0.003$, respectively). Although the delayed treated patients showed a higher frequency in thrombus formation and thromboembolic events (9 of 21 patients −43%) as compared to hyper-early (18 of 82 patients −22%) and early (24 of 96 patients −25%) patients' groups, these differences did not reach statistical significance (Figure 3B). Finally, the three treatment groups did not differ

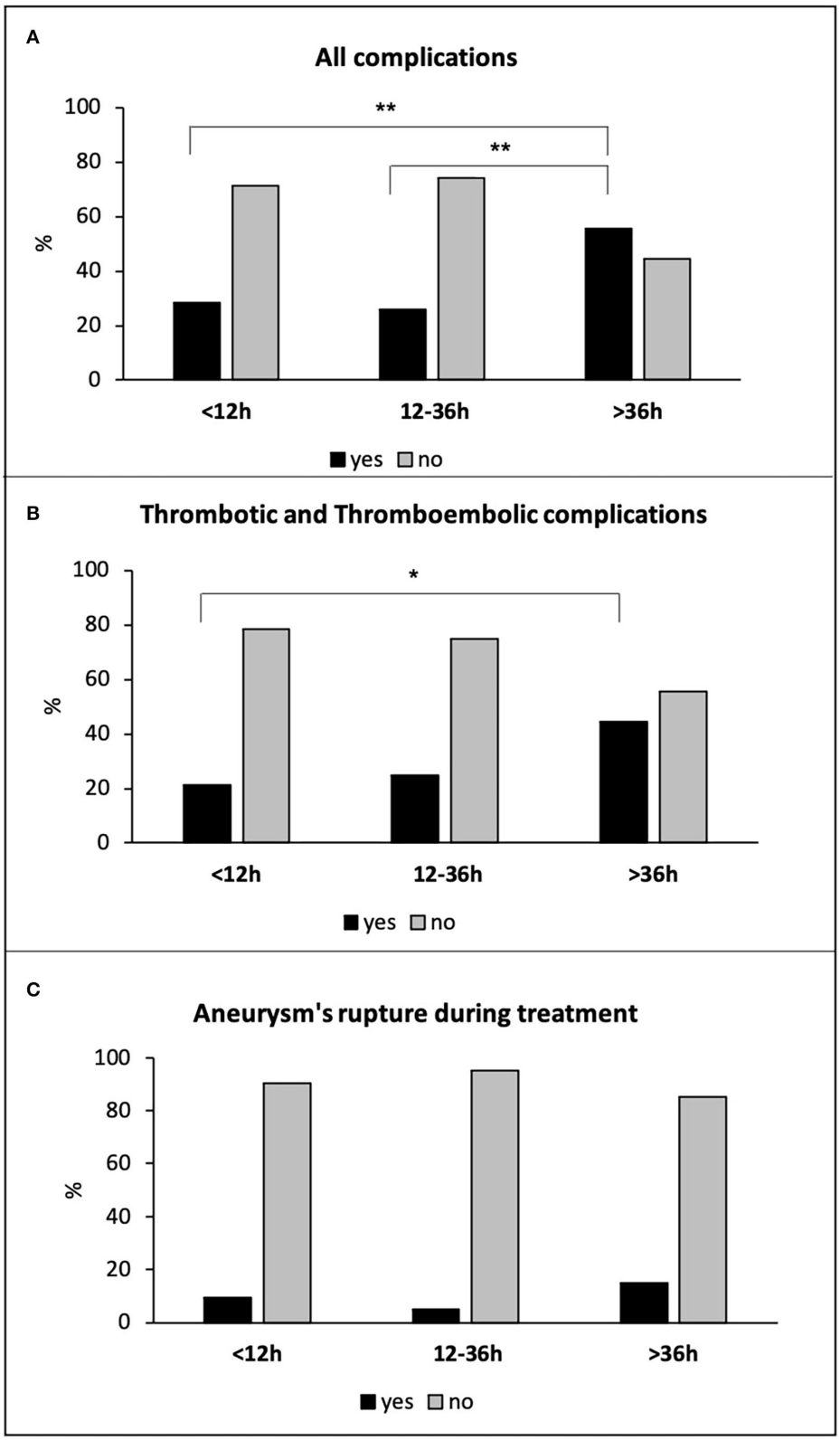

FIGURE 2
All complications **(A)**, thrombotic and thromboembolic complications **(B)**, and aneurysm's rupture during treatment **(C)** in all hyper-early, early, and delayed treated patients. *$p < 0.05$; **$p \leq 0.01$.

TABLE 2 Multivariate logistic regression models for identification of clinically relevant predictors of aneurism treatment complications.

Parameters	Adjusted OR	95% CI	*p*-value
Treatment time from SAH (<12 h, 12–36 h, >36 h)	1.757	1.073–2.879	0.025
Hunt and Hess	1.374	0.976–1.935	0.069
Heparin during procedure	1.737	0.853–3.537	0.128
Modified Fisher	1.059	0.754–1.487	0.742
Rebleeding before treatment	0.350	0.068–1.788	0.207
Aneurysm's location	1.840	0.801–4.227	0.151
Antiplatelets and/or anticoagulant therapy at home	1.915	0.865–4.238	0.109

adjusted OR, adjusted odd ratio; CI, confidence interval; SAH, subarachnoid hemorrhage.

for the incidence of aneurysm's rupture during endovascular treatment: seven of 82 patients −9%; five of 96 patients −5%; and four of 21 patients −19% in the hyper-early, early, and delayed treatment groups, respectively (p = n.s.; Figure 3C).

Discussion

Although endovascular treatment is currently the first-choice treatment in ruptured intracranial aneurysms in most cases (1, 2, 17), some critical issues have not yet been clarified, such as the effects of the timing on safety and effectiveness of the procedure. Our aim was to analyze the incidence of intra-procedural complications in relation to the timing of endovascular treatment, as they can affect morbidity and mortality of these patients.

This study showed that the endovascular treatment of aneurysms more than 36 h after rupture was associated with a significant increased risk of total intra-procedural complications compared to both hyper-early (<12 h) and early (12–36 h) treatments. The delayed treatment group showed particularly a higher rate of thrombus formation and thromboembolic events. The increased risk of total intra-procedural complications in delayed treatment was confirmed, also considering only the subpopulation of patients treated with simple coiling and balloon-assisted coiling. Also in this subpopulation, delayed treated patients showed a higher incidence of thrombus formation and thromboembolic events, compared to hyper-early and early patient's groups. On the other hand, in the total patient's population and in the subpopulation treated with simple coiling or balloon-assisted coiling, no differences were found in the incidence of intra-procedural complications in patients in the hyper-early and early treatment groups.

These data can be explained by the complex platelet aggregation phenomenon observed in patients with SAH (18) and studied in many animals' models (19–27). In most of these studies, the thrombus formation has been evaluated only in the first hours after SAH or at a single time-point. Pisapia et al. (21) examined the microvascular thrombi formation over time in an endovascular perforation mouse model. Using an antithrombin immunostaining, they demonstrated the presence of thrombus in small vessels at 24, 48, 72, and 96 h after SAH with a peak of severity at 48 h. Similarly, Muroi et al. (22) showed a microvascular thrombus formation peak on days 2 and 3 after experimental SAH in the same mouse model using fibrinogen immunostaining. Stein et al. (28) showed similar results in their autopsy series of patients died after SAH, demonstrating that the microclot burden was higher in patients died within 2 days after aneurysm rupture and decreased at days 3 and 4. Many mediators of the inflammation, such as IL-1 and IL-6, and prothrombotic factors, such as platelet-activating factor (PAF), von Willebrand factor (vWF), and β-thromboglobulin, have been involved in the microthrombus formation following SAH (29–32). Hirashima et al. studied the level of PAF in the peripheral blood (30) and in the jugular vein (31) of patients with SAH showing a peak at days 5–9, explaining also the crucial role of platelet aggregation in thrombus formation during endovascular treatment of ruptured aneurysms as demonstrated by Larco et al. (33) in their histopathological study.

Our data are in contrast to the results of Consoli et al. (14), who did not find a difference in the incidence of intra-procedural complications in hyper-early (<12 h), early (12–24 h), and delayed (>24 h) treated patients. This discrepancy may be due to the differences in patients' grouping based on the treatment timing and in complications taken into the consideration between their and our study. While they may have considered only the complications not resolved during the endovascular procedure, we considered all the complications which occurred. In total, 50% of the complications in our series were then resolved endovascularly with only 11% of all patients treated who suffered of a secondary lesion related to the intra-procedural event.

Our study's primary limitation is its retrospective design, which results in a smaller number of patients in the group receiving delayed treatment. On the other side, it might better reflect what actually occurs in daily life, such as more patients in the delayed treatment group having lower Hunt and Hess scores as a result of underestimating the symptoms. The absence

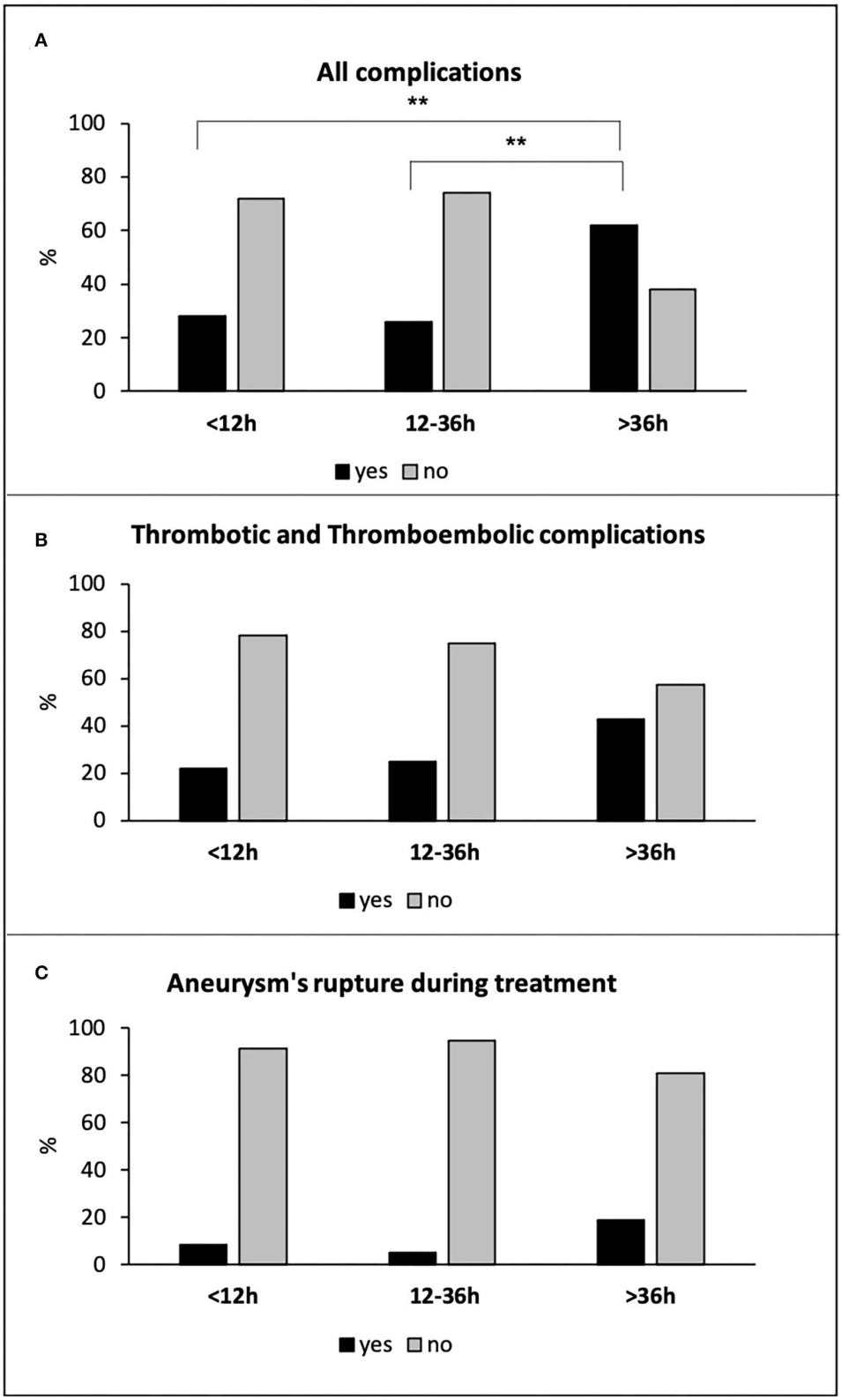

FIGURE 3
All complications **(A)**, thrombotic and thromboembolic complications **(B)**, and aneurysm's rupture during treatment **(C)** in hyper-early, early, and delayed treated patients with simple coiling and balloon-assisted coiling. $^{**}p \leq 0.01$.

of an ACT examination during the endovascular treatment is another limitation.

Neuroinflammation seems to have a crucial role in aneurysm formation and rupture and seems to be involved in vasospasm, hydrocephalus, and headache in patients with SAH (34, 35). It would be interesting to analyze, in a large prospective study, whether a higher level of neuroinflammation is associated with a higher risk of intra-procedural complications during endovascular treatment.

Conclusions

Endovascular treatment of ruptured intracranial aneurysms more than 36 h after SAH seems to be associated with a higher risk of intra-procedural complications, especially thrombotic and thromboembolic events. If available, treatment should be achieved before 36 h after bleeding. A hyper-early treatment performed in the first 12 h after SAH seems to be as safe as between 12 and 36 h.

Data availability statement

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

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 from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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Safety and efficacy of peripheral nerve blocks to treat refractory headaches after aneurysmal subarachnoid hemorrhage – A pilot observational study

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Objectives: Headache after aneurysmal subarachnoid hemorrhage (HASH) is common, severe, and often refractory to conventional treatments. Current treatment standards include medications including opioids, until the pain is mitigated. Peripheral nerve blocks (PNBs) may be an effective therapeutic option for HASH. We conducted a small before-and-after study of PNBs to determine safety, feasibility, and efficacy in treatment of HASH.

Methods: We conducted a pilot before-and-after observational study and collected data for 5 patients in a retrospective control group and 5 patients in a prospective intervention PNB group over a 12-month period. All patients received a standard treatment of medications including acetaminophen, magnesium, gabapentin, dexamethasone and anti-spasmodics or anti-emetics as needed. Patients in the intervention group received bilateral greater occipital, lesser occipital, and supraorbital PNBs in addition to medications. The primary outcome was pain severity, measured by Numeric pain rating scale (NPRS). All patients were followed for 1 week following enrollment.

Results: The mean ages in the PNB group and control group were 58.6 and 57.4, respectively. One patient in the control group developed radiographic vasospasm. Three patients in both groups had radiographic hydrocephalus and IVH, requiring external ventricular drain (EVD) placement. The PNB group had an average reduction in mean raw pain score of 2.76 (4.68, 1.92 p=0.024), and relative pain score by 0.26 (0.48, 0.22 p=0.026), compared to the control group. The reduction occurred immediately after PNB administration.

Conclusion: PNB can be a safe, feasible and effective treatment modality for HASH. Further investigations with a larger sample size are warranted.

KEYWORDS

Headache, subarachnoid hemorrhage, peripheral nerve block, pain, opioid-sparing analgesia

Introduction

Headache after aneurysmal subarachnoid hemorrhage (HASH) is common, severe, and refractory to conventional treatments (1, 2). HASH is often described initially as worst headache of life, and can linger in the background for weeks to months (2). The pathophysiology of headache in aneurysmal SAH (aSAH) remains poorly understood. Initial headache is thought to be from mechanical nociceptor stretching in vascular endothelium and raised intracranial pressure, (3) while sustained headache is thought to be a result of multifactorial activation of the trigeminal-vascular system (3–5). If untreated, HASH can potentially raise ICP due to dysregulated vasodilation by neural activation (6), which can worsen secondary brain injury (SBI). It can also hinder rehabilitation efforts by reducing participation, sleep, mood (7) and negatively impact quality of life (8).

HASH often persists through the time window of delayed cerebral ischemia (DCI) from aSAH, therefore it is imperative that treatment of HASH does not interfere with DCI detection. As it stands, analgesia modalities are limited in these patients. Current pharmacological treatment strategies including acetaminophen, gabapentin, magnesium, steroids, and non-steroidal anti-inflammatory agents (NSAIDs). Each modality is ineffective on its own, and many have significant drawbacks including clouding of neurological status, respiratory suppression and dose-dependent hepatotoxicity or nephrotoxicity. Despite high prevalence and potential deleterious effects of HASH, there is a lack of evidence-based treatment modalities for this disease with only 9% of providers indicating use of a standardized approach for HASH management, for which opioids remain the mainstay (9). Pain trajectories following aSAH are associated with continued opioid use at outpatient follow up (10), which contributes to the ongoing opioid epidemic. Pterygopalatine fossa blockade, recently reported by Smith et al. have recently emerged as a therapeutic option (11), but there continues to be an enormous need for an effective opioid-sparing treatment options in these patients, and more research is needed in this area.

Peripheral nerve blocks (PNBs) have been effective in treatment of acute and chronic headache disorders that involve the trigeminalovascular system, such as migraines, neuralgias, tension-type and chronic headaches (12–14). PNBs reduce headache intensity, duration and opioid usage (14, 15). Recently, a case report described success of a greater occipital nerve block for HASH in two patients (16). We report our pilot before-and-after observational controlled study, which compared patients receiving a bundle of bilateral supraorbital, greater and lesser occipital nerve blocks in addition to medical therapies, with patients receiving medical therapies alone for treatment of refractory HASH. Our hypothesis was that PNBs are safe, feasible, and will reduce HASH severity measured by the numeric pain rating scale (NPRS) immediately, and 1 week after administration.

Methods

Study design

We conducted a before-and-after observational study on a sample of 10 patients with refractory headache after aneurysmal subarachnoid hemorrhage admitted to the neurocritical care unit (NCCU). Headaches were classified as acute headache attributed to non-traumatic subarachnoid hemorrhage according to the 3rd edition of the International Classification of Headache Disorders (ICHD-3). The control group ($n = 5$) received standard-of-care medical treatments according to our HASH treatment protocol, and the intervention group ($n = 5$) received a standardized bundle of bilateral supraorbital, greater, and lesser occipital peripheral nerve blocks, in addition to standard-of-care treatments. The study was conducted between May 2019 and April 2020 at a large tertiary care teaching hospital. Data analysis was retrospective for the control group and prospective for the intervention group. The Institutional Review Board of West Virginia University Hospitals approved this study (IRB approval #1904522761 on 05/23/2019, "Peripheral Nerve Blocks for headache management in Subarachnoid Hemorrhage Population"), including a waiver of consent for the retrospective control group. Procedures were followed in accordance with institutional ethical standards and with the Helsinki Declaration of 1975. Informed consent was obtained from all participants in the prospective group. Inclusion criteria was as follows: ages 18 years or older, confirmed radiographic aSAH, Hunt and Hess grading of 1 or 2, ability to participate in informed consent procedure and presence of a refractory moderate or greater severity headache as defined by NPRS. Pain scores were documented according to the NPRS ranging from 0 to 10 by an intensive care unit nurse. Refractory headache was defined as a moderate or severe headache that persisted or worsened despite two modalities of treatment. Exclusion criteria included history of allergy to any of the medications in the protocol, coagulopathy not amenable to correction, recent suboccipital craniectomy, clinical or radiographic evidence of vasospasm at time of enrollment, history of cirrhosis or acute hepatic failure. Out of 30 patients that were screened, only 5 met inclusion criteria. The most common reason for not meeting inclusion criteria were a Hunt and Hess classification grading of greater than 2 and inability to participate in the informed consent procedure. During the enrollment period, all patients that met inclusion criteria consented for the PNB. All patients in the intervention group received a bundle of PNBs within 24 h of enrollment. All patients were treated for aSAH according to institutional protocols and international guidelines, including definitive aneurysm treatment within 24 h, administration of oral nimodipine and triweekly transcranial doppler ultrasonography (TCD) for vasospasm surveillance.

Pain management

All patients in the study were treated with our standardized multimodal protocol for HASH management, as outlined in Figure 1. Initial treatment included acetaminophen doses up to a maximum of 4 grams daily and intravenous magnesium boluses 1–2 grams, not to exceed 4 grams total in 24 h, followed by scheduled gabapentin and dexamethasone for refractory headaches. Muscle relaxants and anti-emetics were used as adjunct therapy as needed. If HASH remained refractory to this treatment, treatment with opioids was initiated at a starting dose of 5 mg oxycodone every 6 h as needed in the control group and PNBs were administered in the intervention group. All PNBs were administered by two personnel in this study to limit variability, one neurointensivist and one trainee under close supervision of the same neurointensivist. If headaches were refractory to PNB, opioids were also allowed in the intervention group.

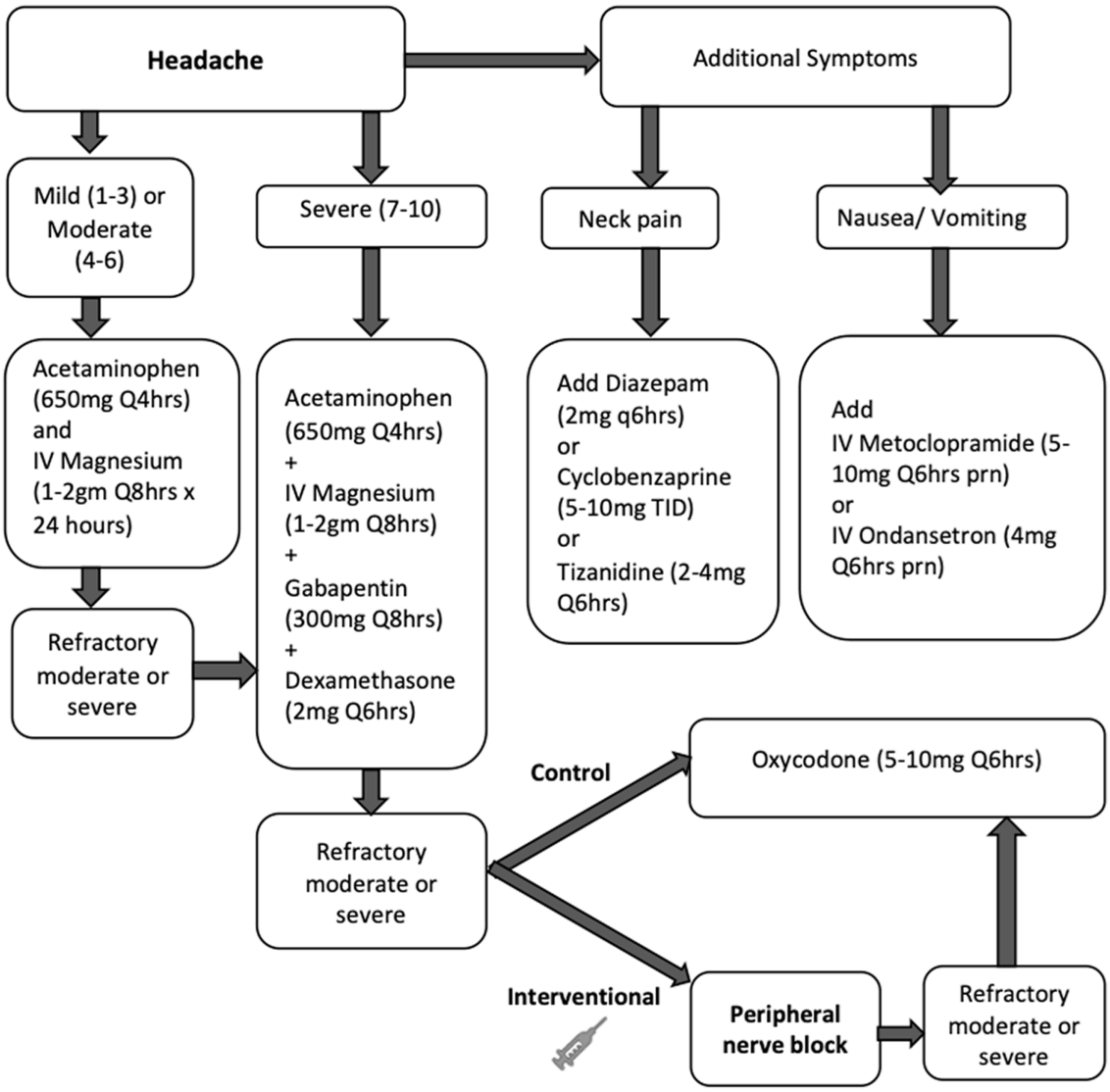

FIGURE 1
Study flow chart for treatment of HASH in the control (medications only) and intervention (peripheral nerve block) groups. Unless specified, medications were administered orally. Refractory headache was defined as a moderate or severe headache that persisted or worsened in intensity 1 h after treatment.

Outcome and data collection

The primary outcome was pain severity, measured by the numeric pain rating scale (NPRS). The secondary outcome was adverse effects including bleeding, infection, hair loss or any reported adverse event due to the PNB or medications used in the trial. We performed a between-group comparison for the outcomes. In the control group, NPRS scores were documented immediately at time of protocol initiation, followed by every 4 h thereafter for 48 h. In the intervention group, NPRS scores were documented immediately before and after the procedure, followed by every 4 h for 48 h. Both groups had a one-time follow up NPRS documented 1 week after enrollment. Data were obtained from electronic medical record (EMR) in the retrospective group and recorded in a Health Insurance Portability and Accountability Act (HIPAA) compliant spreadsheet for the prospective group. Variables included age, Hunt and Hess score, need for mechanical ventilation, NPRS scores, presence or absence of external ventricular drain (EVD), aneurysm treatment and technique, hydrocephalus, intraventricular hemorrhage, or vasospasm during the clinical course, time from SAH to PNB placement, length of stay, complications and disposition. All medications administered were obtained from the medication administration record (MAR) in the EMR. If the patient had left the neurocritical care unit, a member of the research team contacted the patient in person or *via* telephone to obtain the one-week follow up score. There were no protocol changes or deviations during the study period.

Peripheral nerve block procedure

Once HASH was deemed at least moderate in severity and refractory to our standardized treatment algorithm as outlined in Figure 1, all patients in the prospective group participated in an informed consent procedure and received a PNB bundle at the

bedside. Our PNB bundle consisted of bilateral greater occipital, lesser occipital and supraorbital nerve blocks, depicted in Figure 2. Each occipital nerve injection consisted of 3 ml of an equal mixture of 0.5% 5 mg/ml bupivacaine and 4 mg/ml dexamethasone. Each supraorbital nerve injection consisted of 2 ml of 0.5% 5 mg/ml bupivacaine.

Statistical analysis

We used a repeated-measures ANOVA to model pain scores over time in both the intervention group that received the PNB and the control group. We used a Wilcoxon signed-rank test to compare the pre- and post-intervention pain scores. For testing significance, we assumed normality was violated due to the small sample size and used a bootstrap approach in which data are resampled to generate an empirical distribution of the test statistics. For this pilot study, no sample size was determined *a priori* so all consecutive patients fulfilling the inclusion criteria were included during the period. All statistical analysis was performed using R version 4.1.0 and RStudio version 1.3.959. The level of significance was set at 0.05 for all analyses.

Results

Ten patients were included, 5 in the control group and 5 in the intervention (PNB) group. Their demographics are shown in Table 1. The mean ages in the control and PNB groups were 57.4 (median = 59, IQR = 12) and 58.6 (median = 60, IQR = 10), respectively. Mean Hunt and Hess scores in the control and PNB groups were 2.2 (median = 2, IQR = 0) and 2.4 (median = 2, IQR = 0), respectively and mean GCS scores in non-intubated patients were 14.25 in both groups (Control median = 14, IQR = 0.25 and intervention median = 14.5, IQR = 1.25). Three patients in both groups had radiographic hydrocephalus, 4 patients in the control group and 3 patients in the intervention group had IVH, requiring external ventricular drain (EVD) placement. None of the patients in either group underwent ventriculoperitoneal shunting. One patient in the control group developed radiographic vasospasm and 1 patient in each group was intubated during their hospital course in the NCCU. Five patients in the control group and 4 patients in the intervention group underwent aneurysm coiling, while 1 patient in the intervention group underwent aneurysm clipping. Three patients in the control group and 2 patients in the intervention group were discharged home, 2 patients in the control group and 3 patients in the intervention group were discharged to an acute rehabilitation facility. Mean time from aSAH to PNB placement was 7.2 days (median = 6, IQR = 2) in the intervention group. The mean ICU length of stay was 10.6 days in the control group (median = 10, IQR = 2) and 12.8 days in the intervention group (median = 14, IQR = 3). The mean hospital length of stay was 14.2 days in the control group (median = 14, IQR = 0) and 16.2 days in the intervention group

TABLE 1 Demographic variables in control and intervention groups.

Variable		Control group, *n*=5	Intervention group, *n*=5
Age, years (Mean, median, IQR)		57.4, 59, 12	58.6, 60, 10
HH Score (Mean, median, IQR)		2.2, 2, 0	2.4, 2, 0
GCS on admission (Mean, median, IQR)	Intubated	10 T, 10 T, 10 T	10 T, 10 T, 10 T
	Not intubated	14.25, 14, 0.25	14.25, 14.5, 1.25
EVD Placement	No	2 (40%)	2 (40%)
	Yes	3 (60%)	3 (60%)
Hydrocephalus	No	2 (40%)	2 (40%)
	Yes	3 (60%)	3 (60%)
IVH	No	1 (20%)	2 (40%)
	Yes	4 (80%)	3 (60%)
Aneurysm treatment and technique	Coiling	5	4
	Clipping	0	1
Ventriculo-peritoneal shunting		0 (0%)	0 (0%)
Vasospasm	No	4 (80%)	5 (100%)
	Yes	1 (20%)	0 (0%)
Intubated	No	4 (80%)	4 (80%)
	Yes	1 (20%)	1 (20%)
Time from SAH to PNB placement, days (Mean, median, IQR)		N/A	7.2, 6, 2
Complications		0 (0%)	0 (0%)
ICU Length of Stay, days (Mean, median, IQR)		10.6, 10, 2	12.8, 14, 3
Hospital Length of Stay, days (Mean, median, IQR)		14.2, 14, 0	16.2, 16, 3
Disposition	Home	3 (60%)	2 (40%)
	Acute rehab	2 (40%)	3 (60%)
	Skilled nursing facility	0 (0%)	0 (0%)

HH, Hunt and Hess; GCS, Glasgow Coma Scale; IQR, Interquartile range; EVD, External ventricular drain; IVH, Intraventricular hemorrhage; SAH, subarachnoid hemorrhage; PNB, peripheral nerve block; ICU, Intensive care unit. Percentages out of group total have been provided for categorical variables.

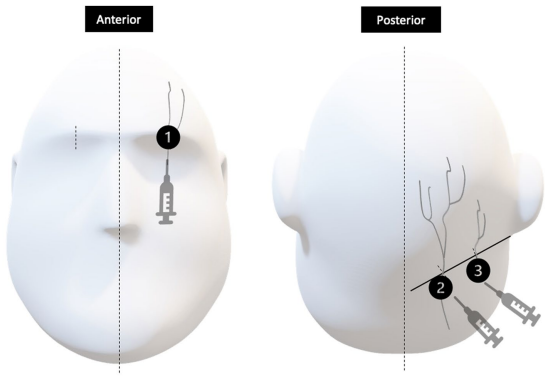

FIGURE 2
Injection sites represented by 1, 2, and 3 correspond to the supraorbital nerve, greater occipital nerve and lesser occipital nerves, respectively. In the anterior view, the supraorbital nerve is identified at about the mid-pupillary line. In the posterior view, greater and lesser occipital nerves exit at approximately one third and two thirds the distance between the external occipital protuberance and the mastoid process, respectively.

(median = 16, IQR = 3). There was no difference in other aspects of management of these patients during the trial period.

To account for variation in patient perception and tolerance of pain when using the raw NPRS, we calculated a scaled variable named relative NPRS by subtracting minimum recorded NPRS from raw NPRS and divided by maximum recorded NPRS for each patient. This transformed each patient's score into a scaled value between 0 for minimum pain and 1 for maximal reported pain. We calculated the comparison of pain scores in both groups from the first time point after intervention, which was at 4 h. From 4 h post-intervention to 1 week, the PNB group had a mean raw pain score of 1.92, and the control group had a mean raw pain score of 4.68 (difference 2.76, $p = 0.024$). From 4 h post-intervention to 1 week, the PNB group had a mean relative pain score of 0.22, and the control group had a mean raw pain score of 0.48 (difference 0.26, $p = 0.026$). The biggest reduction in mean pain scores in the PNB group was between the pre- and post- periods after the PNB was administered, from 0.783 to 0.142 (difference 0.64, $p < 0.003$) and this reduction was sustained at 1 week upon follow-up. The results are demonstrated in a scatterplot of relative NPRS pain scores in both groups over time (Figure 3). A scatterplot of raw pain scores is also included in Supplementary Figure. A solid line shows the mean pain scores of the control group, and a dashed line shows the mean pain scores of the intervention group. The pain scores in the intervention group decrease immediately after the peripheral nerve blocks and remain lower over time, compared to the control group.

We did not find a further significant decrease in pain score at any of the time points compared to the initial decrease post-intervention ($p = 0.9900$). These results are shown in Figure 3.

There were no deviations from our standardized multimodal protocol for HASH management in the control group. Two patients in the intervention group received one-time doses of NSAIDs. One patient in the intervention group received opioids (67.5 morphine equivalent dose) for generalized pain including refractory HASH, prior to enrollment in the study. This patient had a chronic opioid dependence, with an active pre-hospitalization opioid prescription. Of note, this patient did not require opioids for the remainder of her hospitalization. Two patients in the control group received opioids for HASH. Given the small sample size and low incidence of opioid usage for HASH in our cohort, there was no meaningful difference among the two groups in opioid usage (Supplementary Table). There were no reported adverse effects in either group, including bleeding, infection, hair loss or transaminitis due to either PNB or medications used in this study.

Discussion

In this small before-and-after case series of patients with refractory moderate or severe HASH, we found that a one-time bundle of supraorbital, greater occipital and lesser occipital peripheral nerve blocks performed at the bedside to be safe and feasible, as well as efficacious, compared to our standardized medical treatment approach. The relief was immediate and persisted up to a week on our intervention group of 5 patients, suggesting that PNB may a promising adjunct to oral or intravenous medications for patients with HASH, and a valuable treatment modality to study in a large prospective randomized controlled trial. To our knowledge, this is the first prospective study describing efficacy of PNB to treat HASH.

HASH is common, occurs in a majority of aSAH patients and is difficult to treat. In a cohort of aSAH patients, Morad et al. showed that 89% of patients reported a severe headache during their hospitalization (2). Improvements in emergency medical services, aneurysm treatment options and SBI prevention-focused intensive care unit (ICU) management have improved survival and functional outcomes in aSAH patients (17, 18). Despite these improvements, and a high prevalence of HASH, research in this area is lacking including, phenotypic HASH data, efficacious treatment options and treatment guidelines for providers. In the first cross-sectional worldwide study on HASH, Maciel et al. reported that HASH is recognized as a major

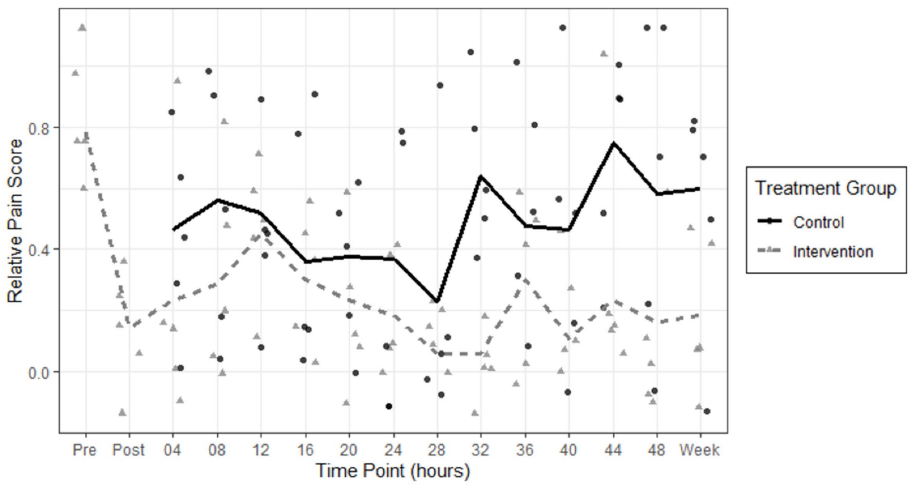

FIGURE 3
Scatterplot of relative NPRS pain scores in the control group (circles) and intervention peripheral nerve block (triangles) groups are shown over 48 h and on one-week follow up. A solid line shows the mean pain scores of the control group, and a dashed line shows the mean pain scores of the intervention group. The pain scores in the intervention group decrease immediately after the peripheral nerve blocks and remain lower over time, compared to the control group.

clinical concern in 87% of providers, opioids are perceived as the most effective analgesic modality, and nearly half the providers prescribe opioids at discharge (9). This is problematic, given the drawbacks of opioid usage in the acute phase of injury following aSAH, as well as longer term, given the high potential for addiction and contribution to the ongoing opioid epidemic. Despite opioid usage, HASH remains unrelieved during hospitalization, with no single agent contributing to substantial HASH relief (19). Research on novel treatment options for HASH is greatly needed.

An effective treatment strategy for HASH likely needs to be multifaceted considering complex pathophysiology, individual pain perception and pain trajectories (10). Although exact mechanism of HASH has not been elucidated, current evidence suggests that blood in the subarachnoid space in the brain and neck can mechanically stretch and irritate trigeminovascular and greater occipital afferent neurons resulting in headache and meningismus (16). Trigeminal release of vasoactive peptides such as calcitonin gene-related peptide (CGRP) can result in vasodilation and activate inflammatory cascades, resulting in sustained activation of the trigeminal sensory system (5) and more prolonged HA (20). This can be compounded by ICP changes as well as cortical spreading depolarizations after SAH (21) that can disrupt ionic gradients, increase neuronal excitability, and further activate the trigeminal sensory system (5). Trigeminal and cervical sensory afferents converge in the spinal trigeminocervical complex (TCC), which gives rise to second-order trigeminothalamic tract neurons. Treatments targeting afferent input into the TCC, such as local perineural application of analgesia and steroids through PNB, may reduce afferent input into and excitability of second-order neurons. Such treatments may decrease central sensitization and alleviate both frontal and occipital HASH (16, 22, 23). Robust animal models have been used to understand HA pathophysiology including trigeminal sensory processing, and animal treatment models have led to substantial advancement in HA therapeutics (24).

Though numerous HASH treatment options exist, nearly all of them have disadvantages that limit their usage in the aSAH population, many having dose-dependent side effects. Acetaminophen and magnesium can be useful adjuncts but are often ineffective on their own (25). Risk of hepatic injury with doses greater than 3–4 grams a day limits dosing of acetaminophen in patients with inadequate HASH relief. Combination therapies with butalbital and caffeine are commonly associated with medication-overuse headaches if discontinued, therefore not ideal choices. Opioids can be sedating thus mask subtle neurological changes, falsely raise alarms for worsening neurological examinations resulting in unnecessary testing, produce hypercapnia (2) or hypotension that can be deleterious in dysregulated brain and compound secondary brain injury. In addition, opioids can result in nausea, vomiting, ileus, or urinary retention which again can raise ICP, contribute to medication-overuse headaches as well as long term dependence and addiction. Gabapentin and anti-epileptic drugs can be good adjuncts and work synergistically to reduce opioid dosing but can also reduce level of arousal in patients monitored closely for DCI (3, 26, 27). A majority of these adverse effects are dose-dependent. Triptans, serotonin 1B/1D receptor agonists and CGRP antagonists may be poor choices as they vasoconstrict cerebral vasculature (6), have case reports of association with reversible cerebral vasoconstriction syndrome and can theoretically worsen DCI in aSAH patients (28). The use of CGRP-modulating therapies in acute conditions such as traumatic brain injury and SAH continues to be explored (29, 30). Data on the effectiveness and safety of NSAIDs are limited in HASH, with over 50% of providers stating they rarely or never used NSAIDS in this setting (9), likely due to perceived risk of worsening bleeding. Systemic dexamethasone is often reserved for refractory cases due to systemic adverse effects of hyperglycemia, reduced sleep, and possible interference with wound healing. Effective HASH treatments are needed, and more non-pharmacological treatment approaches are needed to limit dose-dependent side effects of many of the current treatments.

PNBs are efficacious for treatment of a variety of headaches including occipital neuralgias, migraines, tension headaches and cervicogenic headaches (12, 14, 31), that share similar pathophysiological basis. Efficacy, toxicity and drug content of nerve blocks have been studied using mice models (32). In a case report composed of two patients with HASH, greater occipital PNB was found to provide effective analgesia and significantly reduced the need other medications (16). Smith et al. found bedside pterygopalatine fossa blockade to be efficacious for treatment of HASH and described their findings (11). Data from our observational study indicates that using PNB for HASH may be similarly feasible and effective. Our pilot study is the first to our knowledge that investigated PNBs to treat HASH and aims to add to the limited literature that exists in this important field.

Our study has numerous strengths, including prospective nature of the intervention arm and strict adherence to a standardized treatment protocol in both groups, so there was minimal confounding from dosages or timing of other treatments. Given variation in perception in pain among the general population, using an individualized pain score in addition to raw pain scores is also a strength. All patients were followed up at 1 week after enrollment, so we were able to show there was still benefit at that time point. Importantly, there is growing research that patients with HASH follow discrete pain trajectories (10), and pain trajectories can predict generation of chronic pain (9, 33). In our preliminary study, we found that PNB appeared to alter this trajectory immediately after administration, therefore it is plausible that it may alter and development of chronic HASH in some patients. The ability to perform PNBs at the bedside without specialized equipment allows this treatment modality to be used even in resource-scare environments. Many anesthesia and neurology residencies in North America provide procedural training in PNBs, therefore ease of locating a credentialed healthcare provider with relevant training and expertise may allow more widespread use of this modality to treat HASH. Scalp blocks including peripheral nerve blocks are routinely placed in the operating room by anesthesiologists and/or neurosurgeons for awake craniotomies and are considered low-risk (34).

Limitations of this before-and-after study include single-center observational study design combining retrospective (control group) and prospective data, as well as small sample size. We suspect that the small sample size may have played a role in being unable to detect a significant difference in opioid usage among the two groups. Despite strict adherence to a standardized protocol in both groups, uncaptured differences between the study periods or unblinded nature of the study may have contributed to differences in outcomes, including a placebo effect in the intervention group. It is also possible that patients that received a PNB may have been part of a discrete HASH pain trajectory cohort, that would have experienced improvement in pain scores at 7 days regardless of interventions. Headache phenotypes were not

recorded in this study, which are important for future HASH studies. Only short-term 1 week follow-up information was available in our study group. We limited enrollment to patients that could communicate pain scores to us verbally, therefore our study population was limited to lower severity aSAH patients. Larger studies should be carried out on higher-grade aSAH patients that are able to endorse headaches to increase generalizability. Though we did not utilize repeat PNBs or alternate local anesthetics in patients with recurrent refractory HASH, this should be a consideration in future studies.

Conclusion

Our small before-and-after observational study suggests that peripheral nerve blocks can be a safe, feasible and effective treatment option for headaches after aneurysmal subarachnoid hemorrhage. Further prospective investigations with a larger sample size are necessary.

Key points

Question

Do peripheral nerve blocks help to relieve refractory headaches after subarachnoid hemorrhage (HASH)?

Findings

HASH is a global challenge among survivors, with a few effective treatment options. Peripheral nerve blocks appear feasible, reduce pain immediately after administration and provides sustained pain relief for up to a week compared to conventional medical treatment.

Meanings

PNBs can be conducted safely at the bedside, appears feasible and efficacious for treatment of refractory HASH in our small before-and-after observational study.

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 Review Board of West Virginia University Hospitals approved this study (IRB approval #1904522761 on 05/23/2019, "Peripheral Nerve Blocks for headache management in Subarachnoid Hemorrhage Population"), including a waiver of consent for the retrospective control group. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SR: conceptualization, investigation, methodology, project administration, supervision, writing—original draft, and writing—review and editing. NS: data curation, project administration, writing—original draft, and writing—review and editing. AN: investigation, project administration, and writing—review and editing. JG: methodology, resources, and writing—review and editing. CJ: data curation, formal analysis, methodology, software, validation, visualization, and writing—review and editing. 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1122384/full#supplementary-material

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Sex-specific extracerebral complications in patients with aneurysmal subarachnoid hemorrhage

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Background: Extracerebral complications in patients with aneurysmal subarachnoid hemorrhage (aSAH) often occur during their stay at the neurocritical care unit (NCCU). Their influence on outcomes is poorly studied. The identification of sex-specific extracerebral complications in patients with aSAH and their impact on outcomes might aid more personalized monitoring and therapy strategies, aiming to improve outcomes.

Methods: Consecutive patients with aSAH admitted to the NCCU over a 6-year period were evaluated for the occurrence of extracerebral complications (according to prespecified criteria). Outcomes were assessed with the Glasgow Outcome Scale Extended (GOSE) at 3 months and dichotomized as favorable (GOSE 5–8) and unfavorable (GOSE 1–4). Sex-specific extracerebral complications and their impact on outcomes were investigated. Based on the results of the univariate analysis, a multivariate analysis with unfavorable outcomes or the occurrence of certain complications as dependent variables was performed.

Results: Overall, 343 patients were included. Most of them were women (63.6%), and they were older than men. Demographics, presence of comorbidities, radiological findings, severity of bleeding, and aneurysm-securing strategies were compared among the sexes. More women than men suffered from cardiac complications ($p = 0.013$) and infection ($p = 0.048$). Patients with unfavorable outcomes were more likely to suffer from cardiac ($p < 0.001$), respiratory ($p < 0.001$), hepatic/gastrointestinal ($p = 0.023$), and hematological ($p = 0.021$) complications. In the multivariable analysis, known factors including age, female sex, increasing number of comorbidities, increasing World Federation of Neurosurgical Societies (WFNS), and Fisher grading were expectedly associated with unfavorable outcomes. When adding complications to these models, these factors remained significant. However, when considering the complications, only pulmonary and cardiac complications remained independently associated with unfavorable outcomes.

Conclusion: Extracerebral complications after aSAH are frequent. Cardiac and pulmonary complications are independent predictors of unfavorable outcomes. Sex-specific extracerebral complications in patients with aSAH exist. Women

suffered more frequently from cardiac and infectious complications potentially explaining the worse outcomes.

KEYWORDS

subarachnoid hemorrhage, extracranial complications, gender medicine, outcome, delayed cerebral ischemia, stroke

Introduction

In patients with aneurysmal subarachnoid hemorrhage (aSAH), the high mortality and morbidity are not only associated with the initial bleeding but also with intracerebral secondary complications, such as rebleeding, delayed cerebral ischemia (DCI), and hydrocephalus (1). Similar to intracerebral complications, extracerebral complications are frequent (with reviews finding cardiac injury in ∼36%, arrhythmias in ∼35%, and acute respiratory distress syndrome in ∼4–18% of patients covering multiple studies) (2). Cardiovascular and pulmonary complications are the most frequent and are associated with a sudden and sustained increase in systemic catecholamines, which can lead to organ dysfunction, hypoxemia, hyperglycemia, and an inflammatory state with the release of cytokines (3). In particular, cardiac complications and markers of cardiac injury have been shown to be associated with unfavorable outcomes and the occurrence of DCI (4) with other studies proving the benefit of combined multi-organ dysfunction evaluation for the prediction of outcomes (5). Fever, anemia, and hyperglycemia have also been found to be associated with increased mortality and poor outcomes (6).

Sex-specific differences exist in almost every aspect of a disease. Women are more likely to be affected by aSAH (7–10) possibly due to the intrinsic weakness of the vessel walls, collagen, and elastin interference factors, as well as hormonal aspects (11, 12). Furthermore, aneurysm location itself also appears to be associated with sex (13, 14), with more aneurysms located along the internal carotid artery in female subjects and along the anterior cerebral artery in male subjects. However, so far, while complications after aSAH have been elucidated in various studies, the presence of sex-specific extracerebral complications during the stay at the neurocritical care unit (NCCU) is less investigated.

In this retrospective study, we focus on the extracerebral consequences of aSAH, particularly on sex-specific complications during the stay at the NCCU and their influence on outcomes. The identification of these might aid personalized management and treatment strategies.

Materials and methods

We retrospectively reviewed the medical records of all consecutive patients with aSAH admitted to the NCCU of the University Hospital Zurich over a 6-year period (January 2016–December 2021). All adults (≥18 years old) admitted with aSAH (i.e., with imaging evidence of a ruptured aneurysm) were eligible for inclusion. Exclusion criteria were as follows: (1) patients with only unruptured, traumatic, fusiform, dissecting, or mycotic aneurysms and (2) patients' written or documented oral refusal to have their data analyzed for research projects. The study was performed in accordance with the ethical standards laid down in the 2013 Declaration of Helsinki. The local ethics committee approved the study. STROBE guidelines were used to draft the manuscript.

Patients' population and management

Patients were treated according to the latest AHA/ASA guidelines (15). These include the following: (1) early aneurysm securing by surgical or endovascular means; (2) external ventricular drain insertion (EVD) (BACTISEAL® EVD Catheter, CODMAN, Johnson & Johnson, Raynham, MA, USA) in case of enlargement of the third ventricle and the temporal horns of the lateral ventricles (i.e., ventriculomegaly with signs of acute occlusive hydrocephalus) for the monitoring of intracerebral pressure (ICP) in unconscious and comatose patients; and (3) insertion of invasive multimodal neuromonitoring, including cerebral microdialysis (CMA 70, CMA Microdialysis, Solna, Sweden), brain tissue oxygenation monitoring (LiCox system, Integra Neurosciences, Plainsboro, NJ), and continuous electroencephalography in case of prolonged impaired consciousness either due to the severity of the disease itself or due to the need for deep sedation during the vasospasm phase.

At least until day 14 after aSAH—during the vasospasm phase, all patients (irrespective of initial clinical or radiographic grade) are monitored and treated at the NCCU. In the case of symptomatic vasospasm confirmed by CT-angiography with corresponding clinical deterioration or corresponding perfusion deficit upon perfusion imaging, controlled arterial hypertension is induced by the administration of norepinephrine. In case of non-response to hemodynamic therapy, intraarterial spasmolysis—available 24 h per day—is performed.

Data collection

Data collection was performed by scanning the electronic health records (KISIM-TM; Cistec® Zurich, Switzerland) for demographic characteristics, and clinical course during the ICU stay.

Demographic data collected were sex, age, and presence of comorbidities, based on the Charlson Comorbidity Index (CCI) (16) (i.e., history of myocardial infarction, congestive heart failure, peripheral vascular disease, history of the cerebrovascular event, dementia, chronic pulmonary disease, rheumatologic disease,

gastric ulcer, liver disease, diabetes with or without chronic complications, kidney disease, and history of cancer). The severity of bleeding was assessed by the WFNS and Fisher scale. Complications during the stay at the NCCU were collected in an organ system-specific manner (Supplementary material 1) as follows:

- Cardiovascular (including acute coronary syndrome, Takotsubo syndrome, arrhythmic disorders, and other cardiovascular disturbances);
- Pulmonary (including acute respiratory distress syndrome, aspiration pneumonia, ventilator-associated pneumonia, hospital-acquired pneumonia, and chronic obstructive pulmonary reactivation);
- Hepatic and gastrointestinal (paralytic ileus, peptic ulcer, abdominal compartment syndrome, mesenteric ischemia, acute on chronic liver failure, transaminitis, acute pancreatitis, and cholestatic injury);
- Renal (including acute kidney injury);
- Infections (including urogenital infections, catheter-related bloodstream infection, and sepsis/septic shock);
- Electrolyte disturbances (including hypokalemia, hyperkaliemia, hypomagnesemia, hypermagnesemia, hypophosphatemia, and hyperphosphatemia; sodium disorders are excluded);
- Sodium disorders (including diabetes insipidus, cerebral salt wasting syndrome, and syndrome of inappropriate antidiuretic hormone secretion);

TABLE 1 Univariate analysis: demographics/characteristics*.

		Male	Female	*p*-value	OR	95% CI
		125 (36.4)	218 (63.6)			
Age (mean ± SD)		54.38 ± 11.6	59.15 ± 13.8	<0.01	1.028	1.011–1.046
Length of stay ICU [median (IQR)]		14 [12, 22]	15 [10, 22]	0.58		
CCI [median (IQR)]		0 [0, 2]	0 [0, 1.25]	0.71		
WFNS	1	38 (30.4)	78 (35.8)	0.44		
	2	28 (22.4)	43 (19.7)			
	3	3 (2.4)	10 (4.6)			
	4	28 (22.4)	40 (18.3)			
	5	28 (22.4)	47 (21.6)			
GOSE at 3 months	1	17 (13.8)	43 (20.0)	0.18		
	2	3 (2.4)	9 (4.2)			
	3	21 (17.1)	32 (14.9)			
	4	7 (5.7)	26 (12.1)			
	5	22 (17.9)	23 (10.7)			
	6	22 (17.9)	17 (7.9)			
	7	13 (10.6)	41 (19.1)			
	8	18 (14.6)	24 (11.2)			
Aneurysm location (anterior)		102 (81.6)	169 (77.5)	0.37		
Fisher	1	4 (3.2)	9 (4.1)	0.99		
	2	8 (6.4)	16 (7.4)			
	3	56 (44.8)	87 (40.1)			
	4	57 (45.6)	105 (48.4)			
ICH		37 (29.6)	58 (26.6)	0.55		
Ventriculomegaly		65 (52.0)	114 (52.3)	0.95		
IVH		87 (69.0)	154 (70.6)	0.78		
Treatment modality (clipping)		60 (48.0)	99 (45.4)	0.31		
DCI		39 (31.2)	59 (27.1)	0.41		

*Univariate logistic regression evaluating the association of demographics and clinical features to sex. Data shown as number (%) unless otherwise stated. SD, standard deviation; IQR, interquartile range; OR, odds ratio; CI, confidence interval; ICU, intensive care unit; CCI, Charlson Comorbidity Index; WFNS, World Federation of Neurosurgeons Society; GOSE, Glasgow Outcome Scale Extended; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; DCI, delayed cerebral ischemia.

TABLE 2 Univariate analysis: complications*.

	Male	Female	*p*-value	OR	95% CI
Any	92 (73.6)	174 (79.8)	0.19		
Cardiac	20 (16.0)	61 (28.0)	0.01	2.040	1.163–3.579
Acute coronary syndrome	9 (7.2)	11 (5.1)	0.41		
arrhytmogenic	11 (8.8)	40 (18.4)	0.02	2.329	1.148–4.725
Tako-Tsubo	2 (1.6)	14 (6.4)	0.06		
Pulmonary	64 (51.2)	93 (42.7)	0.13		
Infectious	20 (16.0)	55 (25.2)	0.04	1.771	1.004–3.125
Urinary tract infection	6 (4.8)	37 (17.0)	<0.01	4.054	1.660–9.903
Other	8 (6.4)	9 (4.1)	0.36		
Sepsis	7 (5.6)	14 (6.4)	0.76		
Hepatic/gastrointestinal	5 (4.0)	15 (6.9)	0.28		
Renal	8 (6.4)	12 (5.5)	0.73		
Acute-on-chronic renal failure	3 (2.4)	5 (2.3)	0.95		
Acute renal failure	2 (1.6)	4 (1.8)	0.87		
Rhabdomyolysis	2 (1.6)	1 (0.5)	0.31		
Polyuria	0 (0.0)	2 (0.9)	0.99		
Electrolytes	39 (31.2)	72 (33.0)	0.73		
Sodium	36 (28.8)	70 (32.1)	0.52		
Other	3 (2.4)	3 (1.4)	0.49		
Hematologic	16 (12.8)	30 (13.8)	0.80		
Extracerebral hemorrhage	7 (5.6)	10 (4.6)	0.68		
Thrombosis	5 (4.0)	14 (6.4)	0.35		
Thrombocytopenia	3 (2.4)	8 (3.7)	0.52		
Other coagulopathy	3 (2.4)	2 (0.9)	0.29		

*Univariate logistic regression evaluating the association of complications to sex. Data are shown as numbers (%). OR, odds ratio; CI, confidence interval; SD, standard deviation; IQR, inter-quartile range.

- Hematologic (including hemorrhagic shock and active bleeding but not in the cerebral nervous system);
- Thromboembolic events (including deep vein thrombosis, intravascular catheter-related thrombosis, and pulmonary embolism).

The outcome is reported using the Glasgow Outcome Scale Extended (GOSE) extracted from routine follow-up consultations at 3 months (which include a neurological examination, as well as a description of current occupation including the percentage of working capability). A dichotomized GOSE in favorable (GOSE 5–8) and unfavorable (GOSE 1–4) was considered in the analysis, as in previous studies (10, 17). After excluding infarction caused by aneurysm securing, DCI was defined as a cerebral infarction on CT scans or magnetic resonance images, combined with either clinical deterioration (new focal neurological deficit or GCS decrease of 2 points) and/or impaired perfusion in CT- or MR perfusion (18, 19).

Statistical analysis

Statistical analysis was performed using SPSS version 26. Data were dichotomized by sex (male vs. female) or outcome (favorable vs. unfavorable). Descriptive statistics are reported as counts/percentages, mean ± standard deviation (SD), or as median including the interquartile range (IQR) as appropriate. All continuous data were tested for normality using Shapiro–Wilk's test. Univariate logistic regression was used to find variables associated with sex and unfavorable outcomes. Multivariate analysis was performed based on the univariate analysis to correct results for the differences in clinical characteristics with unfavorable outcomes as a dependent variable. Respective odds ratios (OR) including 95% confidence intervals (95%-CI) are only shown for significant associations. The significance level was set at a *p*-value of <0.05.

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TABLE 3 Univariate prediction: unfavorable outcome*.

Demographics	*p*-value	OR	95% CI
Age	<0.01	1.047	1.029–1.066
Sex (female)	0.02	1.698	1.078–2.674
LOS_ICU	0.09		
CCI	<0.01	1.357	1.147–1.606
WFNS	<0.01	1.866	1.595–2.183
Aneurysm location (anterior)	0.68		
Fisher	<0.01	4.541	2.999–6.878
ICB	<0.01	3.637	2.175–6.083
Ventriculomegaly	<0.01	3.857	2.444–6.088
IVH	<0.01	5.208	3.011–9.006
Treatment modality (clipping)	0.97		
DCI	0.02	1.783	1.100–2.888
Complications			
Cardiac	<0.01	4.206	2.380–7.433
Pulmonary	<0.01	6.612	4.092–10.686
Infectious	0.49		
Hepatic/gastrointestinal	0.02	3.348	1.178–9.520
Renal	0.46		
Electrolytes	0.30		
Hematological	0.02	2.171	1.126–4.185

*Univariate logistic regression for the prediction of unfavorable outcomes. SD, standard deviation; IQR, inter-quartile range; OR, odds ratio; CI, confidence interval; LOS ICU, length of stay intensive care unit; CCI, Charlson Comorbidity Index; WFNS, World Federation of Neurosurgeons Society; GOSE, Glasgow Outcome Scale Extended; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; DCI, delayed cerebral ischemia.

TABLE 4 Multivariate prediction without (base model) and with complications: unfavorable outcomes*.

Basemodel	*p*-value	OR	95% CI
Age (per year increase)	<0.01	1.037	1.014–1.060
Sex (female)	0.02	1.943	1.097–3.442
CCI (per point increase)	0.03	1.235	1.019–1.497
WFNS (per step increase)	<0.01	1.633	1.360–1.960
Fisher (per step increase)	<0.01	2.995	1.871–4.794
Basemodel + cardiac			
Age (per year)	<0.01	1.036	1.014–1.060
Sex (female)	0.06	1.748	0.978–3.123
CCI (per point increase)	0.07	1.201	0.987–1.463
WFNS (per step increase)	<0.01	1.555	1.289–1.877
Fisher (per step increase)	<0.01	3.052	1.886–4.939
Cardiac complications	0.02	2.196	1.108–4.352
Basemodel + pulmonary			
Age (per year)	<0.01	1.035	1.011–1.059
Sex (female)	<0.01	2.594	1.389–4.847
CCI (per point increase)	0.05	1.22	0.998–1.492
WFNS (per step increase)	<0.01	1.508	1.243–1.830
Fisher (per step increase)	<0.01	2.72	1.668–4.434
Pulmonary complications	<0.01	4.719	2.625–8.484
Basemodel + hepatic/gastrointestinal			
Age (per year)	<0.01	1.038	1.015–1.061
Sex (female)	0.03	1.885	1.060–3.350
CCI (per point increase)	0.03	1.237	1.022–1.499
WFNS (per step increase)	<0.01	1.609	1.338–1.933
Fisher (per step increase)	<0.01	3.030	1.889–4.859
Hepatic/gastrointestinal	0.24	2.100	0.610–7.239
Basemodel + hematologic			
Age (per year)	0.01	1.039	1.016–1.062
Sex (female)	0.03	1.931	1.087–3.432
CCI (per point increase)	0.04	1.223	1.008–1.484
WFNS (per step increase)	<0.01	1.619	1.348–1.944
Fisher (per step increase)	<0.01	3.077	1.906–4.937
Hematologic	0.11	1.899	0.866–4.165

*Multivariate logistic regression for the prediction of unfavorable outcomes either using known predictors (Basemodel) or including systemic complications. OR, odds ratio; CI, confidence interval; LOS ICU, length of stay intensive care unit; CCI, Charlson Comorbidity Index; WFNS, World Federation of Neurosurgeons Society.

Results

Overall, 343 patients fulfilled the inclusion criteria. Of these, 63.6% were women ($N = 218$). Women were older than men ($p = 0.002$, an average of 5 years). In addition, no differences by sex were found considering the presence of comorbidities, the severity of bleeding, radiographic findings on the first CT scan (presence of intracerebral hemorrhage, ventriculomegaly, and intraventricular hemorrhage), and treatment modality (coiling/ clipping), as shown in Table 1.

The extracerebral complications are listed in Table 2. More women than men suffered from cardiac complications ($p = 0.013$), particularly arrhythmic disorders ($p = 0.019$). Infectious diseases, overall, were more frequent in women than men ($p = 0.048$). More women suffered from urogenital tract infections ($p = 0.002$). Pulmonary complications were frequent, but no sex-related differences were found. Female sex also remained an independent predictor of cardiac complications after correction for age ($p = 0.037$, OR 1.837, 95% CI 1.036–3.257) but not for infectious complications when corrected for age ($p = 0.054$).

Considering outcomes, female sex, age, CCI, WFNS, and Fisher grading were associated with unfavorable outcomes in the univariate analysis. Considering the extracerebral complications, cardiac, pulmonary, hepatic/gastrointestinal, and hematologic complications were associated with unfavorable outcomes. In the multivariate analysis, increasing age, WFNS, and Fisher grading remained independent predictors of unfavorable outcomes irrespective of the addition of extracerebral complications. When

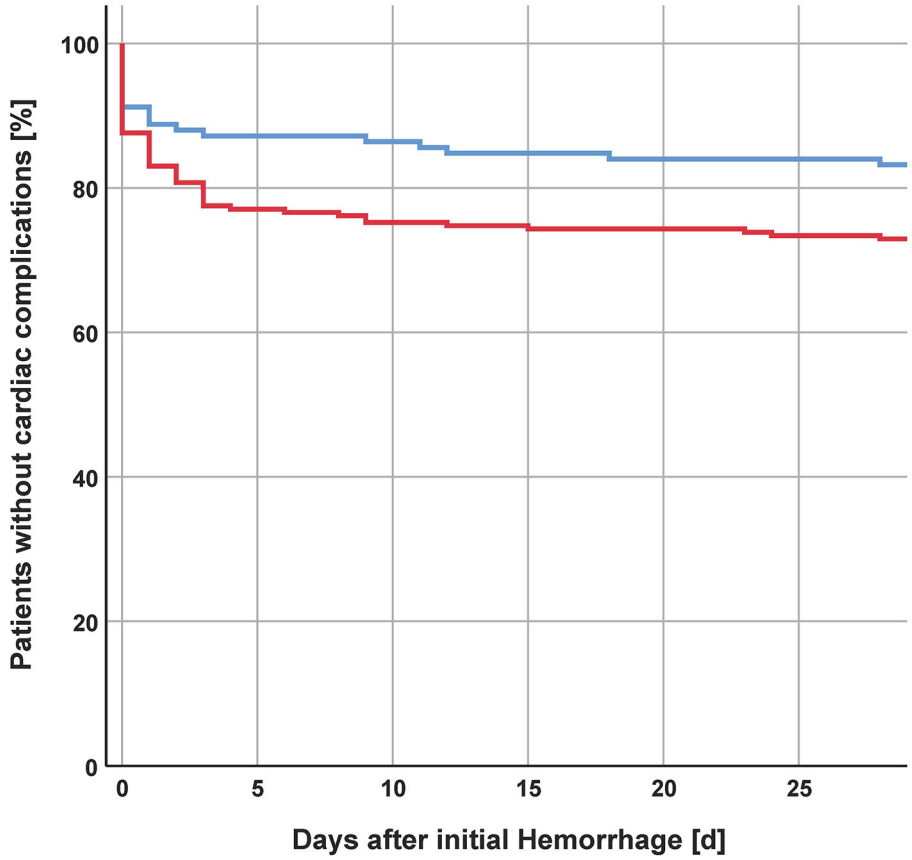

FIGURE 1
Incidence of cardiac complications after initial hemorrhage.

these were added, aside from the above-mentioned known predictors, only pulmonary and cardiac complications remained independent predictors of unfavorable outcomes (Table 3). Sex was an independent predictor of unfavorable outcomes when considered univariately in the base model (excluding extracerebral complications) as well as in the multivariable analysis when adding pulmonary, hepatic/gastrointestinal, or hematologic complications. Interestingly, however, the female sex was not an independent predictor of unfavorable outcomes when including cardiac complications in the base model (Table 4) possibly due to the high association between sex and cardiac complications ($p = 0.01$, OR 2.040, 95% CI 1.163–3.579).

Discussion

In this study, we investigated the frequency of extracerebral complications in patients suffering from aSAH with a particular focus on sex-related differences and their influence on outcomes. Extracerebral complications in patients with aSAH are frequent. Wartenberg et al. described at least one medical complication in 79% of patients with aSAH (6). Similarly, Solenski et al. reported that all the patients recruited had one or more medical complications (20). We found that both sexes frequently suffered from complications (female: 79.8%, male 73.6%). We found cardiac and pulmonary complications to be the most frequent complications in this study population. Similar to prior reports, they were independent predictors of unfavorable outcomes (21–24). No specific subtype of pulmonary complication was associated with significantly worse outcomes, confirming prior reports (22). A catecholamine storm following acute brain injury has been proposed to lead to extracerebral complications by means of hypoxemia, hyperglycemia, and inflammatory state due to the release of pro-inflammatory cytokines (25). A similar mechanism could also explain the complications found in aSAH.

Cardiac complications and the combination of multi-organ dysfunction after aSAH have been shown to be associated with unfavorable outcomes (4, 5). However, whether extracerebral complications occur in a sex-specific manner remains poorly investigated. In our cohort, women suffered more frequently from cardiac complications even after correction for their older age. This difference was mostly based on the higher frequency of arrhytmogenic complications in female subjects. Interestingly, both the absolute frequency, as well as the lack of sex-related difference in the frequency of Takotsubo syndrome, differs from current reviews most likely due to the need for a transthoracic echocardiogram for its diagnosis, which is only ordered in patients with clinical suspicion (26). As previously described, women presented a worse outcome after aSAH (10). Possibly the difference in cardiac complication frequency might explain this difference. In

our cohort, cardiac complications occurred mostly in women and mostly within the first 4 days after the initial hemorrhage (Figure 1). aSAH leads to an acute increased sympathetic nervous system activity with an increased release of catecholamines (27). This increased activity is also associated with cardiac complications and in particular Takotsubo syndrome (26). Some studies even report the beneficial effects of beta-blockers in patients with aSAH (28, 29). Standardized use of beta-blockers in aSAH, however, has not been established yet. Patients at risk for symptomatic vasospasm and DCI receive controlled arterial hypertension to improve cerebral perfusion. Induced hypertension may lead to serious adverse events, such as cardiac arrhythmia, myocardial infarction, pulmonary edema, brain edema, hemorrhagic infarction, and rebleeding (30). These adverse effects of induced hypertension might be potentiated in patients who already suffered cardiac complications/injury prior to its induction.

In the study population, women were more likely to suffer from infections, particularly urogenital infections, during their stay at the NCCU. This finding is in line with previous reports (31, 32). Anatomical differences and the use of bladder catheters might increase the risk of infections in women. This finding suggests that the use of bladder catheters should be carefully evaluated, and removal—in female patients, should be reconsidered on a daily basis in order to prevent the development of urogenital infections.

Strengths and limitations

Our study has several strengths. First, we collected data on a large number of extracerebral complications. Second, we decided to focus on the currently poorly described presence of sex-specific extracerebral complications. Our findings are of clinical relevance and might help to improve the outcomes of patients with aSAH. There are also limitations to our study. First, this is a retrospective single-center study, limiting its generalizability. Second, despite the large number of extracerebral complications collected, some of the interests might not have been investigated, permitting only speculations on the reported differences by sex. Third, we limited our analysis to the duration of stay at the NCCU (at least the first 14 days after the initial bleeding) with no information on complications that developed later on.

Conclusion

Extracerebral complications during the stay at the NCCU after aSAH are frequent. Cardiac and pulmonary complications are predictors of unfavorable outcomes. There are sex-specific extracerebral complications. Women more commonly suffer from cardiac and infectious complications. Patients with prior cardiac injury might benefit from personalized management when at risk of symptomatic vasospasm/DCI with either closer evaluation for further cardiac injury or possibly lower blood pressure target values. Due to the increased risk of urogenital infections in women, the use of bladder catheters should be carefully evaluated, and early removal should be advised.

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 Kantonale Ethik-Kommission Zürich. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SBö: conceptualization, statistical analysis, critical revision, and data interpretation. SBe: data acquisition, writing—original draft, and data interpretation. LH: writing—original draft and data acquisition. FN and FC: critical revision and data acquisition. GB: supervision, writing—review and editing, project administration, and conceptualization. EK: supervision, writing—review and editing, and data interpretation. 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1098300/full#supplementary-material

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Association between hemoglobin-to-red blood cell distribution width ratio and hospital mortality in patients with non-traumatic subarachnoid hemorrhage

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Background: In patients with ischemic stroke, low hemoglobin-to-red blood cell distribution width ratio (HRR) was associated with an increased risk of mortality. However, it was unknown in the non-traumatic subarachnoid hemorrhage (SAH) population. The purpose of this study was to examine the association between baseline HRR and in-hospital mortality in patients with non-traumatic SAH.

Methods: Non-traumatic SAH patients were screened out of the Medical Information Mart for Intensive IV (MIMIC-IV) database between 2008 and 2019. The Cox proportional hazard regression models were utilized to analyze the association between baseline HRR and in-hospital mortality. Restricted cubic splines (RCS) analysis was utilized to determine the relationship curve between hospital mortality and the HRR level and examine the threshold saturation effect. We further applied Kaplan–Meier survival curve analysis to examine the consistency of these correlations. The interaction test was used to identify subgroups with differences.

Results: A total of 842 patients were included in this retrospective cohort study. Compared with individuals with lower HRR Q1 ($\leq$7.85), the adjusted HR values in Q2 (7.86–9.15), Q3 (9.16–10.16), and Q4 ($\geq$10.17) were 0.574 (95% CI: 0.368–0.896, $p = 0.015$), 0.555 (95% CI: 0.346–0.890, $p = 0.016$), and 0.625 (95% CI: 0.394–0.991, $p = 0.045$), respectively. The association between the HRR level and in-hospital mortality exhibited a non-linear relationship ($p < 0.05$). The threshold inflection point value of 9.50 was calculated using RCS analysis. When the HHR level was lower than 9.50, the risk of in-hospital mortality rate decreased with an adjusted HR of 0.79 (95% CI: 0.70–0.90, $p = 0.0003$). When the HRR level was higher than 9.50, the risk of in-hospital mortality almost hardly increased with the increase in the HRR level (adjusted HR = 1.18, 95% CI: 0.91–1.53, $p = 0.2158$). K-M analysis showed that patients with low HRR levels had significantly higher in-hospital mortality ($p < 0.001$).

Conclusion: There was a non-linear connection between the baseline HRR level and in-hospital mortality. A low level of HRR could increase the risk of death in participants with non-traumatic SAH.

KEYWORDS

hospital mortality, hemoglobin-to-red blood cell distribution width ratio, non-traumatic subarachnoid hemorrhage, intensive care unit, MIMIC-IV

Introduction

Subarachnoid hemorrhage (SAH) is a common form of stroke in the intensive care unit (ICU) and a potentially devastating illness (1). It affects nearly 10 percent of every 1,00,000 individuals and accounts for nearly 5% of all strokes each year (2, 3). However, long-term disability and mortality from SAH accounted for 27% of all stroke-related potential years of life lost before the age of 65 years (4). Although the optimal management of SAH has improved, hospital mortality and severe disability are still high (5).

Inflammatory reactions play an important role during the early brain injury induced by SAH and significantly affect the outcomes (6). Experiments have suggested that the mechanism leading to this situation may be extravasated red blood cells in the subarachnoid space undergoing degradation, releasing a host of bioactive and pro-inflammatory properties including hemoglobin (Hb), methemoglobin, and bilirubin (7, 8). Vasoactive factors and inflammation are released, exacerbating brain edema, oxidative stress damage, and cell apoptosis, leading to disruption of the blood–brain barrier (9, 10). Hemoglobin reflects the patient's degree of anemia, and red-blood-cell distribution width (RDW) reflects the heterogeneity in the sizes of erythrocytes (11, 12). In the inflammatory state, the lifespan of red blood cells is shortened, leading to anemia and an increase in RDW.

Previous studies have shown that RDW was a parameter reflecting inflammation (13, 14) and related to the outcomes of SAH patients (15–19). In addition, Hb is an important component of the complete blood count and related to nutritional status (20) and immune response (21). However, the level of RDW and Hb may be affected by many factors, such as medications, nutritional status, oxidative stress, and blood transfusion (13, 22–24). Therefore, Hb/RDW (HRR) is a relatively good parameter for reducing the impact of the factors mentioned. HRR is an easily obtained parameter. Previous investigations have shown that HRR was associated with inflammation (25–27). In recent years, more and more evidence has shown that low level of HRR was closely related to significantly deteriorating prognosis in many critically ill patients, such as coronary heart disease, sepsis, and ischemic stroke (28–30). However, the relationship between HRR and mortality in patients with non-traumatic SAH is lacking.

In this study, we aim to test the association between baseline HRR and hospital mortality among critically ill patients with non-traumatic SAH.

Materials and methods

Data sources

The study data were downloaded freely from a large publicly accessed database called Medical Information Mart for Intensive Care (MIMIC-IV) (31). This database contains information on patients admitted to the Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2019. Posterior to the completion of the National Institutes of Health (NIH) training course and the Protecting Human Research Participants test, one researcher Junhong Wang obtained approval to exploit the database (Record ID, 45677587). The study was carried out following the Helsinki Declaration guidelines and was reviewed and approved by the Massachusetts Institute of Technology and the Institutional Review Board of BIDMC. All data were anonymous to protect patient privacy, and the need for informed consent was waived. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (32).

Study population

A total of 1,142 patients with non-traumatic SAH were selected based on the record of ICD-9 code 430 and ICD-10 code I60. Patients who met the requirements were selected to undergo analysis: (1) first ICU admission; (2) age > 18 years. The exclusion criteria were as follows: (1) ICU patients with a length of stay <24 h and (2) participants who had missing hemoglobin or red blood cell distribution width value. Finally, 842 patients were included in this study (Figure 1).

Data extraction

Structured Query Language (SQL) and PostgreSQL are used to extract the following variables from the MIMIC-IV database in our study: (1) demographic variables include sex, age, and ethnicity. (2) vital signs include the heart rate, respiratory rate (RR), mean blood pressure (MBP), systolic blood pressure (SBP), diastolic blood pressure (DBP), percutaneous oxygen saturation (SpO_2), and temperature. (3) Comorbidities include myocardial infarction, congestive heart failure, chronic pulmonary disease, paraplegia, hypertension, diabetes, and sepsis. (4) Laboratory variables include glucose, platelet, white blood cell (WBC) count, calcium, mean corpuscular hemoglobin (MCH), prothrombin time (PT), activated partial thromboplastin time (APTT), Hb, and RDW. The first test of RDW and Hb were included within 24 h after entering the ICU. (5) Severity at admission was identified *via* the Glasgow coma score (GCS) and World Federation of Neurosurgical Societies (WFNS). (6) Delayed cerebral ischemia (DCI), hydrocephalus, Length of ICU stay, length of the hospital, and in-hospital mortality. (7) HRR was calculated using the following formula: HRR = Hb (g/L)/RDW (%) (29, 30, 33).

Endpoints

The outcome was in-hospital mortality, which was described by the patient's survival status at the moment of discharge from the hospital.

Statistical analysis

The continuous variates were displayed as average ± standard deviation (SD) or mid-value (interquartile range). The Student's *t*-test or Mann–Whitney *U*-test was used according to the normality of the distribution. Categorical variates were displayed as case quantity (%), and the chi-square test (or Fisher's exact approach)

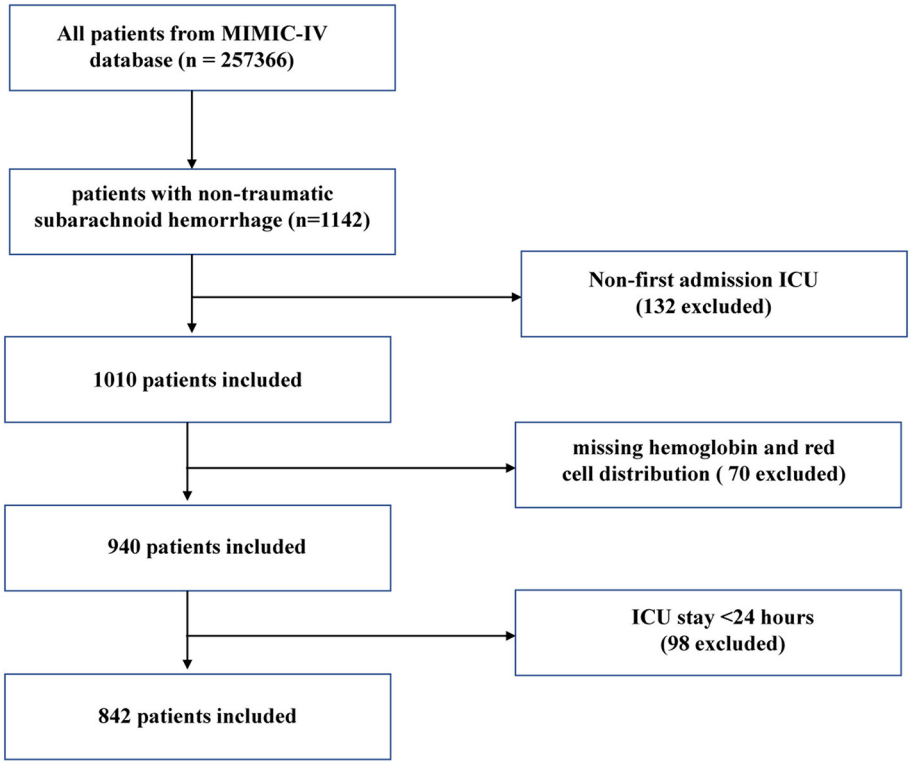

FIGURE 1
Flow chart of the study. MIMC-IV, Medical Information Mart for Intensive Care IV; ICU, intensive care unit.

was utilized for analyses of the difference between the different HRRs (four quantiles) (29).

To reduce the interference of potential confounding factors on in-hospital mortality, univariate and multivariate Cox proportional hazard regression analyses were performed. The screening of confounders was based on the following criteria: (1) The factor had a significant impact (>10%) on the research variate. (2) Certain factors may have a significant impact on the outcome variate based on previous experiences. (3) For univariate analysis, our team modified the variates ($p < 0.05$). In the multivariate case, we performed several statistical models to ensure that the results were stable. In the crude model, no variables were adjusted. In model I, age, sex, and ethnicity variables were adjusted, while model II further adjusted other 16 variables, including heart rate, RR, WBC, PT, APTT, congestive heart failure, Charlson comorbidity index, endovascular therapy, sepsis, norepinephrine, vasopressin, ventilation, GCS, WFNS, DCI, and hydrocephalus.

Restricted cubic spline analysis was employed to determine whether there was a curve relationship between hospital mortality. If the non-linear correlation was observed, a two-piecewise linear regression model was performed to calculate the threshold effect of the HRR on hospital mortality in terms of the smoothing plot (34). The turning point for the HRR was determined using "exploratory" analyses, which is to move the trial turning point along the pre-defined interval and pick up the one which gave maximum model likelihood. We also performed a log-likelihood ratio test and compared the one-line linear regression model with the two-piecewise linear model (35). We used the bootstrap resampling method to calculate the 95% CI for the turning point, as described in the previous analysis (30, 34, 36).

Furthermore, interactions and stratified analyses were conducted using age (<65 and ≥65 years old), sex, WBC counts, myocardial infarction, congestive heart failure, chronic pulmonary disease, renal disease, paraplegia, hypertension, sepsis, endovascular therapy of aneurysm, and GCS (<8 and ≥8), as previously described. Missing values were filled with mean values (37). The details of the missing values are shown in Supplementary Table 1.

A two-tailed p-value of <0.05 was considered to be statistically significant in all analyses. All statistical analyses were carried out using EmpowerStats (http://www.empowerstats.com, version 3.6.1 R software package) software (35).

Results

Baseline characteristics of the study patients

After the screening, 1,010 patients were admitted to the ICU due to non-traumatic SAH for the first time, of whom 842 were selected for the final data analysis (see the flowchart in Figure 1). The distribution of the baseline characteristics of the population according to baseline HRR levels in quartiles is described in Table 1 (Q1: ≤7.85, Q2: 7.86–9.15, Q3: 9.16–10.16, and Q4: ≥10.17). The mean age was 61.2 ± 14.9 years, and ~55.9% of these were women.

TABLE 1 Population characteristics by quartiles of the baseline HRR level.

Variables	Quartiles of HRR					*p*-value
	Total ($n = 842$)	Q1 ($\leq$7.85) ($n = 211$)	Q2 (7.86–9.15) ($n = 209$)	Q3 (9.16–10.16) ($n = 211$)	Q4 ($\geq$10.17) ($n = 211$)	
Demographic						
Female, *n* (%)	471 (55.9)	136 (64.5)	151 (72.2)	111 (52.6)	73 (34.6)	<0.001
Age, years	61.2 ± 14.9	64.4 ± 15.2	63.3 ± 16.0	59.8 ± 13.5	57.3 ± 13.5	<0.001
Ethnicity, *n* (%)						0.022
Asian	32 (3.8)	8 (3.8)	9 (4.3)	8 (3.8)	7 (3.3)	
White	507 (60.2)	109 (51.7)	128 (61.2)	135 (64)	135 (64)	
Black	68 (8.1)	30 (14.2)	16 (7.7)	13 (6.2)	9 (4.3)	
Other	235 (27.9)	64 (30.3)	56 (26.8)	55 (26.1)	60 (28.4)	
Vital signs						
Heart rate, beats/min	78.7 ± 13.1	81.5 ± 14.3	77.3 ± 12.4	77.2 ± 12.4	78.7 ± 12.7	<0.001
SBP, mmHg	125.3 ± 12.9	123.4 ± 14.3	126.1 ± 12.6	125.2 ± 13.6	126.5 ± 10.8	0.069
DBP, mmHg	64.3 ± 8.9	61.7 ± 9.2	62.2 ± 8.6	65.7 ± 7.7	67.5 ± 8.7	<0.001
MBP, mmHg	82.5 ± 8.6	80.2 ± 8.9	81.9 ± 8.6	83.9 ± 8.3	84.1 ± 8.0	<0.001
RR, times/min	18.2 ± 3.2	18.9 ± 3.5	17.9 ± 2.9	17.7 ± 3.1	18.0 ± 3.2	<0.001
Temperature, °C	37.0 ± 0.5	37.0 ± 0.7	37.0 ± 0.4	37.0 (36.8, 37.3)	37.0 (36.8, 37.3)	0.383
SpO_2, %	97.5 ± 1.9	97.8 ± 2.0	97.8 ± 1.8	97.2 ± 2.1	97.2 ± 1.7	<0.001
Comorbidities, *n* (%)						
Myocardial infarction	61 (7.2)	21 (10)	17 (8.1)	11 (5.2)	12 (5.7)	0.203
Congestive heart failure	70 (8.3)	34 (16.1)	13 (6.2)	16 (7.6)	7 (3.3)	<0.001
Chronic pulmonary disease	122 (14.5)	38 (18)	36 (17.2)	26 (12.3)	22 (10.4)	0.072
Paraplegia	139 (16.5)	44 (20.9)	38 (18.2)	32 (15.2)	25 (11.8)	0.075
Renal disease	54 (6.4)	35 (16.6)	9 (4.3)	5 (2.4)	5 (2.4)	<0.001
Hypertension	423 (50.2)	105 (49.8)	117 (56)	101 (47.9)	100 (47.4)	0.269
Diabetes	39 (4.6)	15 (7.1)	10 (4.8)	9 (4.3)	5 (2.4)	0.142
Sepsis	424 (50.4)	127 (60.2)	116 (55.5)	98 (46.4)	83 (39.3)	<0.001
Charlson comorbidity index	4.0 (3.0, 6.0)	5.0 (4.0, 8.0)	5.0 (3.0, 6.0)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	<0.001
Laboratory results						
Platelets, 10^9/L	230.0 (187.0, 280.8)	219.0 (161.5, 284.5)	238.0 (188.0, 279.0)	232.0 (191.5, 276.0)	231.0 (193.5, 281.5)	0.186

(Continued)

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TABLE 1 (Continued)

Variables	Quartiles of HRR					*p*-value
	Total ($n = 842$)	Q1 ($\leq$7.85) ($n = 211$)	Q2 (7.86–9.15) ($n = 209$)	Q3 (9.16–10.16) ($n = 211$)	Q4 ($\geq$10.17) ($n = 211$)	
WBC, 10^9/L	12.9 (9.9, 16.5)	12.9 (8.9, 17.2)	12.5 (10.0, 15.9)	12.7 (10.0, 15.3)	14.0 (10.8, 17.3)	0.046
Hemoglobin, g/L	12.2 ± 1.9	9.9 ± 1.4	11.7 ± 0.8	12.8 ± 0.7	14.2 ± 1.1	<0.001
RDW, %	13.9 ± 1.6	15.6 ± 2.1	13.6 ± 0.8	13.3 ± 0.7	12.9 ± 0.8	<0.001
Glucose, mg/dl	130.9 (113.4, 153.5)	128.6 (110.6, 158.7)	135.6 (114.0, 150.8)	129.0 (113.2, 151.0)	131.8 (114.6, 154.0)	0.756
Calcium, mg/dl	8.7 (8.3, 9.1)	8.6 (8.2, 9.1)	8.7 (8.3, 9.1)	8.7 (8.4, 9.0)	8.9 (8.6, 9.2)	<0.001
MCH, pg	30.5 (29.2, 31.8)	29.5 (27.1, 30.9)	30.4 (29.3, 31.6)	30.7 (29.6, 31.8)	31.2 (29.9, 32.4)	<0.001
PT, s	12.6 (11.7, 13.8)	13.6 (12.2, 15.8)	12.5 (11.8, 13.4)	12.3 (11.5, 13.1)	12.4 (11.6, 13.4)	<0.001
APTT, s	28.8 (25.9, 33.1)	29.6 (26.9, 36.7)	28.4 (25.6, 32.8)	27.8 (25.6, 31.6)	29.1 (26.4, 32.0)	0.003
Therapy, *n* (%)						
Norepinephrine	30 (3.6)	17 (8.1)	5 (2.4)	4 (1.9)	4 (1.9)	<0.001
Vasopressin	8 (1.0)	4 (1.9)	0 (0)	1 (0.5)	3 (1.4)	0.193
Ventilation	429 (51.0)	130 (61.6)	111 (53.1)	95 (45)	93 (44.1)	<0.001
Clipping of aneurysm	35 (4.2)	6 (2.8)	10 (4.8)	13 (6.2)	6 (2.8)	0.410
Endovascular therapy of aneurysm	201 (23.9)	44 (20.9)	60 (28.7)	53 (25.1)	44 (20.9)	0.050
Scores						
GCS	12.0 (7.0, 14.0)	10.0 (7.0, 14.0)	10.0 (6.0, 14.0)	13.0 (8.0, 14.0)	13.0 (7.5, 14.0)	<0.001
WFNS						0.003
I	127 (15.1)	24 (11.4)	27 (12.9)	39 (18.5)	37 (17.5)	
II	172 (20.4)	32 (15.2)	33 (15.8)	50 (23.7)	57 (27)	
III	115 (13.7)	29 (13.7)	26 (12.4)	34 (16.1)	26 (12.3)	
IV	185 (22.0)	51 (24.2)	57 (27.3)	39 (18.5)	38 (18)	
V	243 (28.9)	75 (35.5)	66 (31.6)	49 (23.2)	53 (25.1)	
Outcomes						
Delayed cerebral ischemia	64 (7.60%)	7 (3.32%)	14 (6.70%)	19 (9.00%)	24 (11.37%)	0.014
Hydrocephalus	77(9.14)	19 (9.00%)	18 (8.61%)	16 (7.58%)	24 (11.37%)	0.581
Length of ICU stay, days	7.0 (2.9, 12.9)	5.9 (2.7, 11.9)	7.5 (2.9, 13.8)	6.8 (3.2, 13.8)	7.1 (2.6, 12.7)	0.408
Length of hospital stay, days	11.3 (6.7, 18.7)	11.8 (6.0, 19.9)	12.1 (7.4, 19.3)	10.8 (6.2, 17.1)	10.5 (6.7, 16.4)	0.275
In-hospital mortality	166 (19.7)	71 (33.6)	35 (16.7)	29 (13.7)	31 (14.7)	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; RR, respiratory rate; SpO_2, percutaneous oxygen saturation; HRR, hemoglobin/red cell distribution width; WBC, white blood cell; MCH, mean corpuscular hemoglobin; PT, prothrombin time; APTT, activated partial thromboplastin time; GCS, Glasgow coma score; WFNS, World Federation of Neurosurgical Societies; ICU, Intensive care unit; SAH, subarachnoid hemorrhage.

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TABLE 2 Multivariate cox regression analyses for in-hospital mortality in non-traumatic subarachnoid hemorrhage patients.

Exposure	Non-adjust model		Model I		Model II	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
HRR quartiles						
Q1 (≤7.85)	1 (Ref)		1 (Ref)		1 (Ref)	
Q2 (7.86–9.15)	0.500 (0.333, 0.751)	<0.001	0.522 (0.347, 0.786)	0.002	0.574 (0.368, 0.896)	0.015
Q3 (9.16–10.16)	0.435 (0.282, 0.671)	<0.001	0.489 (0.315, 0.759)	0.001	0.555 (0.346, 0.890)	0.015
Q4 (≥10.17)	0.447 (0.292, 0.686)	<0.001	0.534 (0.342, 0.834)	0.006	0.625 (0.394, 0.991)	0.045
p for trend	0.742 (0.643, 0.855)	<0.001	0.784 (0.676, 0.909)	0.001	0.872 (0.780, 0.974)	0.015
HRR (per 1 increases)	0.861 (0.798, 0.929)	0.001	0.895 (0.828, 0.968)	0.005	0.877 (0.797, 0.964)	0.007

Non-adjusted: no covariates were adjusted.
Model I: adjusted for age, sex, and ethnicity.
Model II: adjusted for age, sex, ethnicity, heart rate, RR, WBC, PT, APTT, congestive heart failure, Charlson comorbidity index, endovascular therapy, sepsis, Norepinephrine, vasopressin, ventilation, GCS, WFNS, delayed cerebral ischemia, hydrocephalus.
RR, respiratory rate; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; GCS, Glasgow coma score; WFNS, World Federation of Neurosurgical Societies; HRR, hemoglobin/red cell distribution width; HR, hazard ratio; CI, confidence interval; Ref, reference.

The demographics, vital signs, comorbidities, laboratory variables and scoring, and other related data according to HRR levels are presented in Table 1. According to Table 1, we found that there were significant differences in age, sex, ethnicity, heart rate, DBP, MBP, RR, congestive heart failure, renal disease, sepsis, WBC, PT, APTT, GCS, and WFNS. Compared with patients in the Q1 group, patients with HRR in Q2, Q3, and Q4 groups were at lower risk of in-hospital mortality and ICU mortality.

The non-survivor group presented lower HRR (median: 8.5 vs. 9.3, $p < 0.001$). Compared with the survivor group, the non-survivor group was older (66.8 ± 14.9 vs. 59.8 ± 14.5 years old, $p < 0.001$) and presented a higher comorbidity incidence, such as congestive heart failure, sepsis, chronic pulmonary disease, Charlson comorbidity index, as well as lower GCS scores (all *p*-values < 0.05) (Supplementary Table 2).

The association between baseline HRR and in-hospital mortality

The univariate analysis demonstrated that age, heart rate, RR, WBC, PT, APTT, sepsis, Charlson comorbidity index, norepinephrine, vasopressin, ventilation, GCS, WFNS were associated with in-hospital mortality (Supplementary Table 3). Table 2 showed an unadjusted and a multivariable-adjusted association between HRR and in-hospital mortality. In model I, age, sex, and ethnicity variables were adjusted, while model II further adjusted other 16 variables, including heart rate, RR, WBC, PT, APTT, congestive heart failure, Charlson comorbidity index, endovascular therapy, sepsis, norepinephrine, vasopressin, ventilation, GCS, WFNS, DCI, hydrocephalus. When HRR was used as a continuous variable, the results showed that HRR was associated with in-hospital mortality (non-adjusted model: HR = 0.861, 95% CI: 0.798–0.929, $p = 0.0001$; Model I: HR = 0.895, 95% CI: 0.828–0.968, $p = 0.0052$; Model II: HR = 0.887, 95% CI: 0.797–0.964, $p = 0.007$). The in-hospital mortality of non-traumatic SAH decreased with a 1-unit increase in HRR. Moreover, as a classification variable, patients with lower HRR levels had significantly increased in-hospital mortality. Compared to the reference group (Q1 ≤ 7.85), the adjusted HR values for individuals in Q2 (7.86–9.15), Q3 (9.16–10.16), and Q4 (≥10.17) were 0.574 (95% CI: 0.368–0.896, $p = 0.015$), 0.555 (95% CI: 0.346–0.890, $p = 0.016$), and 0.625 (95% CI: 0.394–0.991, $p = 0.045$), respectively (*p* for trend = 0.015). Regarding sensitivity analysis, HRR levels were assessed as a continuous and categorical variable, respectively, with in-hospital mortality, yielding consistent results. In addition, the K-M curves contrasting the four groups were displayed in Figure 2.

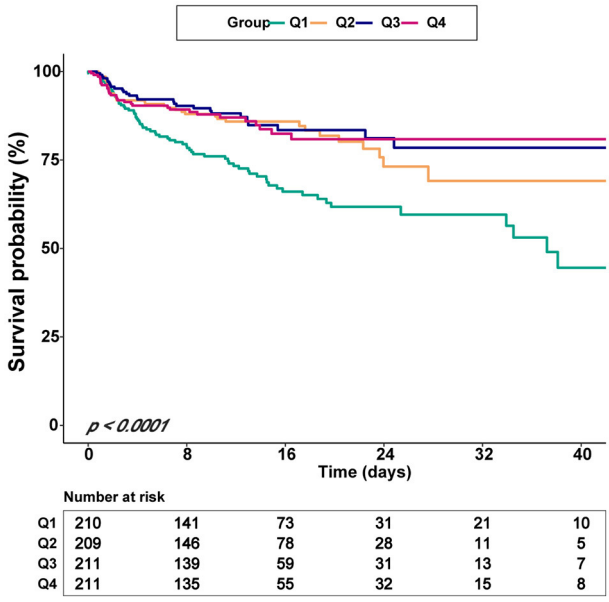

FIGURE 2
Kaplan–Meier survival curves for critically ill patients with non-traumatic SAH based on the baseline HRR level. X-Axis: survival time (days). Y-Axis: survival probability. HRR, hemoglobin/red cell distribution width; SAH, subarachnoid hemorrhage.

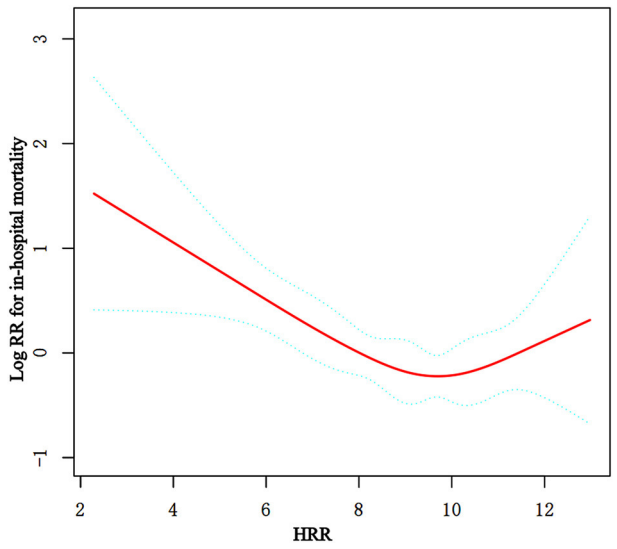

FIGURE 3
Non-linear relationship observed between in-hospital mortality and the baseline HRR level, and the slope changes evidently, which may have a threshold saturation effect. The solid red line represents the smooth curve fit between variables. Blue bands present the 95% confidence interval. The data were adjusted for the variables in Model II in Table 2.

TABLE 3 Threshold-effect analysis of the relationship between the baseline HRR level and in-hospital mortality in non-traumatic SAH patients.

Models	Per-unit increase		
	HR	95%CI	*p*-value
Model I			
One line effect	0.88	0.80–0.96	0.0066
Model II			
Turning point (K)	9.50		
Baseline HRR levels < K	0.79	0.70–0.90	0.0003
Baseline HRR levels > K	1.18	0.91–1.53	0.2158
p-value for LRT test*			0.025

Model I, one-line linear regression model; Model II, two-piece wise linear regression model. Adjusted for age, sex, ethnicity, heart rate, RR, WBC, PT, APTT, congestive heart failure, Charlson comorbidity index, endovascular therapy, sepsis, Norepinephrine, vasopressin, ventilation, GCS, WFNS, delayed cerebral ischemia, hydrocephalus.
HR, Hazard Ratio; CI, confidence interval; LRT, logarithm likelihood ratio test.
*$p < 0.05$ indicates that Model II is significantly different from Model I.

The figure indicated that the survival rate of group Q1 was lower than groups Q2, Q3, and Q4 ($p < 0.0001$).

Analysis of the non-linear relationship between the baseline HRR and in-hospital mortality

After adjusting the variables in Model II, a curve-fitting equation for baseline HRR and death during hospitalization was established using restricted cubic spline analysis. We observed that the association between the HRR level and in-hospital mortality exhibited a non-linear curve (Figure 3). In the threshold analysis, we used a two-piecewise model to fit the link between the baseline HRR level and in-hospital mortality. We found an inflection point at 9.50 (Table 3). On the left side of the inflection point, the HR of HRR was 0.79 (95% CI: 0.70–0.90, $p = 0.0003$). This meant that the risk of in-hospital mortality was reduced by 21% per 1 unit increase. On the right side of the inflection point, the HR was 1.18 (95% CI: 0.91–1.53, $p = 0.2158$). It suggested that the association between HRR and in-hospital mortality was not statistically significant when the level of HRR was more than 9.50. This meant that the risk of in-hospital no longer decreased with increasing HRR. In our study, the *p*-value for the log-likelihood ratio test was 0.025 (Table 3).

Subgroup analysis

The subgroup analysis was conducted to reveal the correlation between HRR and in-hospital mortality across age (<65 and ≥65 years old), sex, WBC counts, myocardial infarction, congestive heart failure, chronic pulmonary disease, renal disease, paraplegia, hypertension, sepsis, endovascular therapy of aneurysm, GCS (<8 and ≥8), and the results are shown in Figure 4. The interaction between the HRR and all subgroup factors was analyzed, and significant interactions were not observed (*p* for interaction > 0.05).

Discussion

In the retrospective observational study, we investigated the relationship between the baseline HRR level and in-hospital mortality among non-traumatic SAH patients and made several important findings. First, we demonstrated that HRR was inversely associated with in-hospital mortality after adjusting for possible confounding factors. Second, we also found a threshold effect. When the HRR was <9.50, the risk of in-hospital mortality decreased with the increase in HRR level. However, patients with progressively higher HRRs above this level did not show any further trend of mortality decreasing. Third, we observed no obvious interaction between the baseline HRR and in-hospital mortality, which indicated that HRR was independently associated with in-hospital mortality in different subgroups, even considering the surgical requirements.

HRR is easily obtained from a routine laboratory database without any external technology or cost and is significantly related to the level of inflammatory reactions (25–27). The HRR itself is not associated with mortality but rather the degree of inflammation that it represents. To the best of our knowledge, the relationship between the level of inflammation and mortality rate has long been a concern of non-traumatic SAH patients. The relationship between HRR and in-hospital mortality remains unknown, which prompted us to carry out the current study. A series of previous studies have demonstrated that a low level of HRR was associated with poor outcomes among multiple malignant diseases (25, 33, 38–41). In recent years, there was mounting evidence that a lower level of HRR was strongly associated with significantly worse

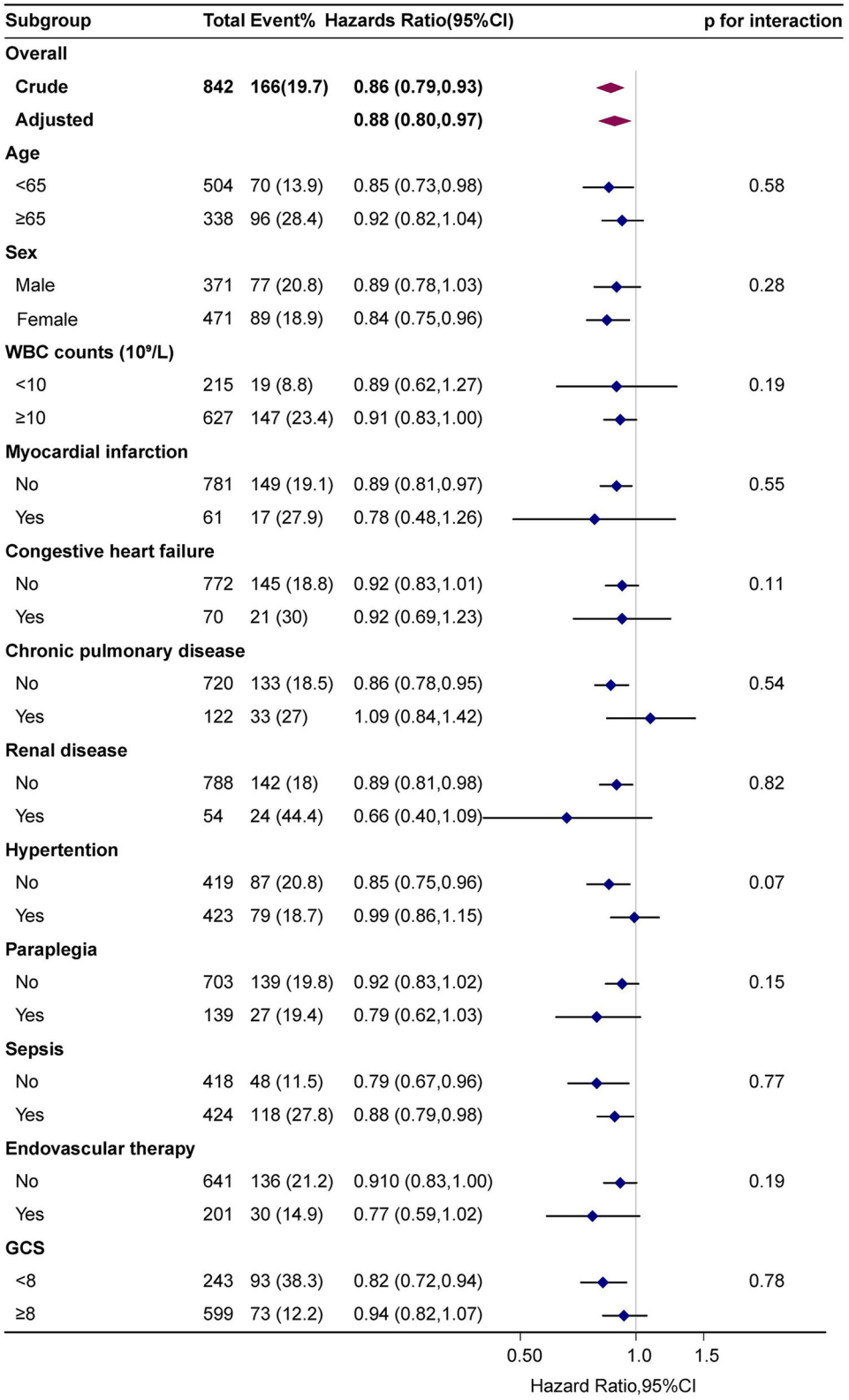

FIGURE 4
Subgroup analyses of the effect of hospital mortality. Adjusted for age, sex, ethnicity, HR, RR, WBC, PT, APTT, congestive heart failure, Charlson comorbidity index, endovascular therapy, sepsis, norepinephrine, vasopressin, ventilation, GCS, WFNS, except the subgroup variable.

outcomes in many critically ill patients, such as coronary heart disease (28), sepsis (29), ischemic stroke (30), and so on. One study with 6,046 participants found that a lower HRR (HRR<10.25) in patients with percutaneous coronary atherosclerotic heart disease was associated with a 1.47-fold increased risk of long-term all-cause mortality. Qu et al. revealed an inverse association between lower HRR (<9.76) and the risk of frailty in elderly patients with coronary heart disease, and HRR was identified as a stronger predictor of frailty than RDW or Hb. In our previous survey, a lower HRR (<5.877) was also observed to be strongly associated with an increased risk of all-cause mortality in individuals with sepsis (29). Moreover, Qin et al. used the MIMIC-IV to determine the relationship between HRR and all-cause mortality in ischemic stroke patients and found that a lower HRR was associated with increased mortality in these patients (30). All the above results indicated that a lower HRR was associated with worse outcomes than a higher HRR. According to the findings above, we hypothesize that low HRR levels may increase the risk of mortality in patients with non-traumatic SAH. More experiments are needed to validate our hypothesis.

Several hypothesized mechanisms have been proposed to explain the reason why lower HRR leads to adverse outcomes in non-traumatic SAH patients. First, higher RDW in the normal range may mean red blood cell disruption or ineffective erythropoiesis (42). Furthermore, a higher RDW level also reflects an underlying inflammatory state and is related to adverse outcomes (43, 44). Forhecz et al. performed a retrospective cohort study involving 195 patients suffering chronic heart failure and found the correlation between RDW and inflammatory markers such as C-reactive protein, interleukin-6, soluble tumor necrosis factor (TNF) receptor I and II (45). Inflammation reactions will damage iron metabolism and inhibit the secretion of erythropoietin, resulting in a decrease in the hemoglobin level (46). In addition, after SAH, it usually triggers a physiological stress response, and increased release of endogenous catecholamine and cortisol, which may lead to secondary brain injury and potential inflammatory complications. Second, the oxygen-carrying capacity mainly depends on the hemoglobin level. The decrease in the hemoglobin value indicates that the oxygen supply of cerebral vessels is significantly reduced, and the oxygen supply of brain tissue is limited, which may lead to vasospasm. Moreover, extravasated red blood cells in the subarachnoid space undergo degradation, releasing a host of bioactive and potentially toxic molecules including hemoglobin, methemoglobin, and bilirubin, which have long been associated with the development of cerebral vasospasm and outcome (7, 8). Vasospasm will seriously affect the prognosis of patients with SAH (11, 12). Third, previous studies have shown that HRR was associated with the risk of frailty risk (26). Dysphagia, systemic infection, or anemia were the main causes of frailty in the early stage of SAH, which may aggravate the condition. Among individuals with lower HRR levels, we consistently noted a higher incidence of sepsis, which also explains this.

Our research has the following strengths: (1) This is the first study to examine the association between baseline HRR levels and in-hospital mortality in participants with non-traumatic SAH. (2) The study used real-world data to design a large-scale and diverse population study. The missing value of HRR was lower, which may reduce the selection bias. (3) We used a 2-piecewise Cox proportional risk regression model to analyze the threshold effect of the relationship between HRR and all-cause mortality. In addition, our findings may help clinicians identify high-risk participants with non-traumatic SAH.

However, the study has some limitations. First, due to its retrospective observational design, and thus, we were only able to provide the association between HRR and hospital mortality, and it is difficult to distinguish the cause and effect. Second, this single-center cohort may not fully represent the general patient population with non-traumatic SAH. Third, due to the limitations of the MIMIC database, missing information that could have affected the model was not collected, such as medications and acute stress. However, it should be noted that the potential results from these variables would bias toward the null, resulting in an undervaluation of the connection between HRR levels and hospital mortality. Four, we analyzed the first HRR record collected during ICU admission, and therefore, the results are limited to a confined period during which HRR was measured. We only collected data on hospitalization, so we only evaluated short-term results. Long-term results should be evaluated through further research. Nevertheless, the relationship between low HRR levels and hospital mortality was revealed.

Conclusions

Therefore, patients with low HRRs should be given more attention, and their in-hospital mortality rate may be higher. This would benefit clinicians and contribute to better decisions.

Data availability statement

The data analyzed in this study was obtained from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, the following licenses/restrictions apply: To access the files, users must be credentialed users, complete the required training (CITI Data or Specimens Only Research) and sign the data use agreement for the project. Requests to access these datasets should be directed to Physionet, https://doi.org/10.13026/7vcr-e114.

Ethics statement

The studies involving human participants were examined and approved by Beth Israel Deaconess Medical Center. To protect patient privacy, all data were de-identified; therefore, the Ethical Committee of the Beth Israel Deaconess Medical Center waived the requirement for informed consent. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing—original draft preparation, writing—review and editing, visualization, and supervision: JW and JL. 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.

Publisher's note

Supplementary material

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Balanced volatile sedation with isoflurane in critically ill patients with aneurysmal subarachnoid hemorrhage – a retrospective observational study

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Introduction: In patients with severe aneurysmal subarachnoid hemorrhage (SAH) deep sedation is often used early in the course of the disease in order to control brain edema formation and thus intracranial hypertension. However, some patients do not reach an adequate sedation depth despite high doses of common intravenous sedatives. Balanced sedation protocols incorporating low-dose volatile isoflurane administration might improve insufficient sedation depth in these patients.

Methods: We retrospectively analyzed ICU patients with severe aneurysmal SAH who received isoflurane in addition to intravenous anesthetics in order to improve insufficient sedation depth. Routinely recorded data from neuromonitoring, laboratory and hemodynamic parameters were compared before and up to 6 days after initiation of isoflurane.

Results: Sedation depth measured using the bispectral index improved in thirty-six SAH patients (–15.16; p=0.005) who received additional isoflurane for a mean period of 9.73±7.56 days. Initiation of isoflurane sedation caused a decline in mean arterial pressure (–4.67 mmHg; p=0.014) and cerebral perfusion pressure (–4.21 mmHg; p=0.013) which had to be balanced by increased doses of vasopressors. Patients required increased minute ventilation in order to adjust for the increase in $PaCO_2$ (+2.90 mmHg; p<0.001). We did not detect significant increases in mean intracranial pressure. However, isoflurane therapy had to be terminated prematurely in 25% of the patients after a median of 30 h due to episodes of intracranial hypertension or refractory hypercapnia.

Discussion: A balanced sedation protocol including isoflurane is feasible for SAH patients experiencing inadequately shallow sedation. However, therapy should be restricted to patients without impaired lung function, hemodynamic instability and impending intracranial hypertension.

KEYWORDS

balanced anesthesia, inhalation anesthetic, isoflurane, bispectral index (BIS), neurocritical care, subarachnoid hemorrhage

1. Introduction

Continuous management of pain, delirium and achievement of conscious sedation have evolved as a pillow of modern critical care therapy (1–3). However, patients with severe aneurysmal subarachnoid hemorrhage (SAH) often require initial deep sedation in order to curb brain edema formation, control cerebral oxygen consumption, and increase convulsive threshold in an attempt to improve cerebral outcome (4–6).

Recently volatile sedation has attracted increased attention in critical care medicine, as newly developed vaporizing systems have made their use safe and feasible outside the operating room (OR) (7, 8). Volatile sedation with its ability to lower the cerebral metabolic rate of oxygen ($CMRO_2$) and shorter awakening and extubation times, offers some potentially desirable features in SAH patients in which prolonged deep sedation is often times needed (7–12). Notably, increasing evidence from experimental animal studies suggests that inhalational anesthetics such as isoflurane have a neuroprotective effect on ischemic brain tissue and positive and intrinsic effects on the occurrence and severity of cerebral vasospasm (13–18). In line with these data, recent studies identified the use of volatile anesthetics during aneurysm repair as an independent predictor of less angiographic vasospasm and less delayed cerebral ischemia in SAH patients (19, 20).

However, the clinical role of volatile sedation in SAH patients in the Neurosurgical Intensive Care Unit (NICU) remains limited and controversial, as a study from Purrucker et al. showed a critical increase in intracranial pressure (ICP), presumably caused by hemodynamic instability following initiation of monotherapy with sevoflurane in patients with acute brain injury (21). In accordance with these findings, short-term use of volatile anesthetics in the OR was associated with episodes of increased ICP either caused by a decrease in mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) or increased regional cerebral blood flow (CBF) (22, 23). On the other hand, three studies found no such critical adverse events particularly no increase in ICP, when patients with acute brain injury were switched to isoflurane mono sedation (24–26). However, the number of patients in these studies were limited, duration of treatment was confined just to several hours, and patient's sedation was switched to an isoflurane monotherapy, thereby causing a high incidence of potentially detrimental side effects like MAP and CPP reduction. Consequently, there is a lack of evidence concerning the safety and feasibility of long-term volatile sedation in patients with SAH.

However, some patients with acute severe aneurysmal SAH display signs of inadequate sedation depths, often times resulting in ventilator asynchrony, patient distress and agitation despite the use of high doses of conventional anesthetics. This inadequate sedation bears the risk of an increased $CMRO_2$ and increased CBF and thereby potentially leads to brain edema formation and intracranial hypertension due to imbalances in cerebral oxygen delivery (4). The use of volatile anesthetics can be considered on an individual basis to achieve adequate sedation according to the *German evidence and consensus based guideline for the management of delirium, analgesia, and sedation in intensive care medicine* published in 2015 (2). Therefore, at our NICU, patients received low-dose volatile isoflurane in addition to the in-house standard of intravenous hypnotic drugs as a therapeutic attempt if deemed necessary to achieve a sufficient sedation depth according to the treating physician's opinion.

In this retrospective study, we analyzed data obtained from our patient data management system (PDMS) enclosing a homogenous cohort of 36 patients with aneurysmal SAH in the NICU receiving a balanced sedation including volatile isoflurane in order to improve inadequately shallow sedation. Here, we report the immediate, short, medium and long-term effects by retrospectively analyzing data in the selected period from 48 h before and up to 144 h after the initiation of isoflurane on neuromonitoring data such as ICP, as well as hemodynamic, respiratory parameters, and laboratory measurements.

2. Methods

2.1. Patients

Ethical approval for this study (project number 20–006) was provided by the Ethical Committee of the Ludwig Maximilian University of Munich on 24 February 2020. The need for written informed consent was waived due the retrospective nature of the study in which all data were processed anonymously using standardized data query. Patient data were collected from the hospital's patient data management system (PDMS) Q-Care ICU (Health Information Management GmbH, Bad Homburg, Germany).

All patients with the main diagnosis of aneurysmal subarachnoid hemorrhage who were hospitalized between August 2015 and November 2018 were identified. In a next step, all patients who had received volatile isoflurane sedation during the course of their ICU treatment were selected for further analysis. Initiation of volatile sedation was left to the discretion of the attending physician when insufficient sedation depth was deemed harmful for the patient's outcome: insufficient depth of sedation as indicated by the Richmond Agitation Sedation Scale (RASS) > −5 or, if implemented, bispectral index monitoring >40 (Infinity® Delta, BISx™ SmartPod, VF 8.4 software, Dräger AG, Lübeck, Germany) despite upper limit doses of intravenous sedatives due to our in-house sedation protocol. However, the following criteria had to be fulfilled before the initiation of additional volatile sedation: Mechanical ventilation, estimated sedation time > 5 days, and external ventricular drainage for ICP measurement in place. Following patients were not seen as suitable for volatile sedation and did not receive volatile sedation: Age < 18 years, ICP elevation above 20 mmHg for more than 5 min in the previous 48 h, pre-existing impaired pulmonary function (e.g., known COPD, partial arterial pressure CO_2 ($PaCO_2$) > 45 mmHg, PaO_2/FiO_2 < 200, positive end-expiratory pressure (PEEP) > 10 cmH_2O, peak inspiratory pressure > 30 cmH_2O), known history or family history of malignant hyperthermia.

2.2. Mechanical ventilation and sedation management

According to our in-house treatment guidelines, respiratory settings according to the guidelines for lung protective ventilation on www.ardsnet.org (mechanical ventilation protocol summary: tidal volume ≤ 6 mL/kg predicted body weight, using the "lower PEEP/higher FiO_2" table) were chosen and settings were adjusted to target values by regular arterial blood gas analysis (PaO_2 70–100 mmHg, $PaCO_2$ 35–45 mmHg, pH 7.35–7.45). Ventilator settings were documented each time a blood gas analysis was performed (at least four times in 24 h).

Patients were sedated according to an in-house standard protocol with continuous infusion of midazolam (0.15–0.7 mg/kg/h) ± propofol (1–4 mg/kg/h) ± ketamine (100–200 mg/h) combined with the analgesic opioid sufentanil (0.5–0.7 µg/kg/h). Volatile sedation was started with the Sedaconda® anesthetic conserving device (ACD-L with dead space of 100 mL) by adding 2–6 mL/h of the pharmaceutical Sedaconda® (isoflurane, both from Sedana Medical AB, Danderyd, Sweden) per inhalation. The administration of isoflurane via the medical device Sedacona® has been approved for inhaled sedation in intensive care without any restriction in duration of therapy by the German pharmaceutical authority BfArM (Bonn, Germany). The dose of inhalational isoflurane was titrated to reach a target RASS of −5 and in case BIS monitoring was established, to establish an bispectral index of 20–40. Expiratory target concentration of 0.2–0.6 vol.% isoflurane was measured by an external gas monitoring device (Vamos®, Dräger AG, Lübeck, Germany). Minimal alveolar concentration (MAC) for a given age was calculated using the following formula: $MAC_{age} = MAC_{40} \times {}^{10-0.00269(age-40)}$ (27).

Isoflurane administration was ceased when need of deep sedation was no longer required. Since the use of volatile anesthetics is contraindicated in patients with increased ICP according to the *German evidence and consensus based guideline* (2) we stopped the administration of isoflurane immediately when ICP was >20 mmHg for more than 5 min.

All patients were screened for other potential severe adverse events (malignant hyperthermia, liver and renal impairment, and ventilation impairment). Therefore, serum liver enzymes, renal functional parameters and markers for acute rhabdomyolysis were tested on a daily basis. In case of a supposed adverse event, the treating physician terminated volatile sedation by individual decision.

2.3. SAH management

SAH treatment followed standardized management protocols. Patients underwent surgical aneurysmal clipping or interventional neuroradiologic coiling as decided by a joint neurovascular committee during the first 24 h following hospital admission. NICU treatment included continuous ICP measurement via an external ventricular drainage (EVD, Integra Life Sciences, Ratingen, Germany). As zero reference point for the EVD transducer we use the external acoustic channel; for measuring invasive blood pressure we used the level of the phlebostatic axis as the optimal measurement location remains debated (28, 29). The EVD was left open to drainage cerebral spinal fluid above a individually defined pressure threshold. The EVD was closed hourly by the nursing staff in order to assess the intracranial pressure. When the ICP was above 20 mmHg for more than 5 min the attending physician was informed. ICP management followed a step-wise protocol including balanced sedation, arterial blood gas homeostasis, targeted CPP management, hypertonic fluids, and surgical craniotomies as described elsewhere (30) in accordance with current guidelines (31, 32).

Patients were neurologically examined twice daily by the treating physician (pupillary reaction, reflex status, muscle tone), pupillary reaction and Glasgow Coma Score (GCS) were additionally checked every hour by the nursing staff. Occurrence of cerebral vasospasm was assessed by daily transcranial Doppler sonography. Cerebral imaging was performed depending on the patient's clinical course. All relevant patient parameters (ICP, MAP, CPP, heart rate, urinary bladder temperature, and laboratory results) were documented via a direct interface with the PDMS. The nursing staff of the NICU validated all hourly measured values and checked for potential measurement errors before the data were transferred to the PDMS.

2.4. Statistical analysis

All data were collected from the NICU PDMS. To investigate immediate, short- mid-, and long-term changes (see below for definition), we calculated the means ± standard deviation (SD) of all documented values available during the respective period for each patient and compared the mean values of all patients obtained before the initiation of isoflurane with the means after the start of therapy. Immediate: One hour before to 1 hour after the initiation of isoflurane. Short-term: -period 6 h to -1 h before isoflurane vs. period +1 h to +6 h after isoflurane, mid-term: −24 h to −1 h vs. +1 to 24 h, long-term: −48 h to −1 h vs. +1 h to +144 h. As cerebral pathomechanisms in SAH vary over time we focused on the actual effects on the induction of balanced volatile sedation during the initial treatment phase on NICU. Therefore, we decided to end the retrospective data analysis after 144 h (6 days), although most patients received isoflurane for a longer period. If fewer than four values were documented in the above-mentioned periods, the patient was excluded from the respective parameter analysis. The number of patients included in the analysis at any time point is given for all investigated parameters. For categorical data, absolute and relative frequencies are given. For statistical analysis, the differences of each patient between the parameters before and after administration of isoflurane were tested for normality using the Shapiro–Wilk or D'Agostino-Pearson test. Normally distributed data were examined with a paired Student's t-test, non-normally distributed data with Wilcoxon matched-pairs signed-ranks Test. Comparison of baseline parameters (period -24 h to -1 h) between patients with or without following premature termination of volatile sedation was performed using a unpaired Student's *t*-test or Mann–Whitney *U*-test. We did not adjust for multiple comparisons; thus, all *value of p*s are descriptive. *p* -values <0.05 were considered as significant. We collected data using Microsoft Excel 2016 and performed statistical evaluation using Prism version 7.2 (Graph Pad Software, San Diego, CA, United States).

3. Results

3.1. Patient demographics and outcome

One hundred and twelve patients were admitted to the NICU of the University Hospital of LMU Munich with the primary diagnosis of aneurysmal SAH between 08/2015 and 11/2018. Thirty-six patients received balanced volatile sedation with isoflurane via the Sedaconda® ACD. The overall mortality in the NICU was generally low, reaching 2.77% (1 out of 36 patients) given the recorded SAH severity with a median of Fisher 4 [interquartile range (IQR, 4 to 4) and WFNS 4 (IQR, 2 to 5)] (Table 1). Volatile sedation was established on average 3 days [IQR, 2 to 5 days] after admission to the NICU. Patients received isoflurane for mean period of 9.73 ± 7.56 days at a dose of 2–6 mL/h (mean 2.74 ± 0.71 mL/h). This corresponded to an expiratory

TABLE 1 Patient's baseline demographic and clinical parameters.

	No.	Age (years)	Sex	Start isoflurane (days after admission)	Indication for discontinued isoflurane	Duration volatile sedation (days)	SAH fischer grade	SAH WFNS grade	Intervention treatment	ICU LOS (days)	Death on ICU
No clinical indication for termination ($n = 27$, 75%)	1	73	Male	5	–	5	4	V	Coil	29	0
	2	76	Female	3	–	7	4	V	Coil	40	0
	3	53	Male	3	-	17	3	I	Clip + Coil	32	0
	4	41	Male	2	–	21	3	IV	Coil	32	0
	5	55	Female	5	–	14	4	II	Coil	27	0
	6	71	Female	2	–	4	4	IV	Clip	26	0
	7	57	Female	1	–	20	4	V	Clip	32	0
	8	58	Female	7	–	13	2	IV	Clip + Coil	17	0
	9	46	Female	2	-	13	3	II	Clip	20	0
	10	80	Female	5	–	5	3	II	Coil	26	0
	11	49	Female	3	–	30	4	IV	Clip + Coil	62	0
	12	37	Female	5	–	6	3	III	Coil	28	0
	13	64	Male	3	–	4	4	V	Coil	26	0
	14	62	Female	9	–	9	4	IV	Clip	26	0
	15	66	Female	12	–	10	4	I	Coil	36	0
	16	50	Female	2	–	4	4	III	Coil + Clip	36	0
	17	52	Male	2	–	21	4	V	FlowDiver.	64	0
	18	63	Female	2	–	12	4	V	Clip	28	0
	19	57	Female	1	–	15	4	V	Coil	34	0
	20	65	Female	5	–	4	4	V	Clip	28	0
	21	51	Female	2	–	22	4	V	Clip	37	0
	22	51	Female	5	–	17	3	II	Clip	40	0
	23	50	Male	1	–	4	4	II	No	40	0
	24	47	Female	2	–	21	3	II	Clip	32	0
	25	45	Female	13	–	12	4	V	Clip	33	0
	26	41	Male	9	–	12	4	II	FlowDiver.	31	0
	27	53	Female	10	–	7	4	V	Coil/WebDev.	16	1

(Continued)

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TABLE 1 (Continued)

	No.	Age (years)	Sex	Start isoflurane (days after admission)	Indication for discontinued isoflurane	Duration volatile sedation (days)	SAH fischer grade	SAH WFNS grade	Intervention treatment	ICU LOS (days)	Death on ICU
Indicated termination of volatile sedation ($n = 9$, 25%)	28	53	Female	11	ICP/LEE	<1 h/5d	4	V	Clip	43	0
	29	55	Female	4	CO_2	33 h	4	V	Coil	31	0
	30	70	Female	15	ICP	14 h	4	IV	Clip	35	0
	31	53	Female	3	ICP	30 h	4	V	Coil	58	0
	32	57	Female	2	CO_2	20 h	4	II	Clip	33	0
	33	49	Female	1	ICP	4	4	V	Coil	26	0
	34	45	Male	0	CO_2	11 h	4	IV	Clip	46	0
	35	51	Male	5	ICP	6	4	IV	Clip	65	0
	36	51	Male	2	CO_2	39 h	4	III	Clip	35	0
Overall cohort		**56 (10.1)**	**10/26 (m/f)**	**3 [2 to 5]**	**5/4 (ICP/CO2)**	**9.73 (7.56)**	**4 [4 to 4]**	**4 [2 to 5]**		**32 [27 to 39]**	**2.77%**

SAH, subarachnoid hemorrhage; ICP, intracranial pressure crisis; LEE, critical liver enzyme elevation; CO2, refractory hypercapnia; Fisher Grade; WFNS grade, World Federation of Neurological Surgeons; ICU, intensive care unit; LOS, length of stay; Interventions/treatment: Clip, aneurysmal clipping; Coil, aneurysmal coiling; FlowDiv., aneurysmal treatment via intraluminal flow diverter; WebDev., aneurysmal treatment via intraluminal web device; Values given for the overall cohort are means (±SD) or median (IQR) as not stated otherwise.

concentration of 0.2–0.6 vol.% and a minimal alveolar concentration (MAC) of approximately 0.19–0.57 for a 56-year old patient (mean age of the cohort).

3.2. Immediate and short-term changes

Within the first hour after the initiation of isoflurane, the mean ICP increased only slightly (−1 h: 10.32 vs. +1 h: 10.5_2 mmHg; $n = 31$; $p = 0.671$; Table 2; Figure 1). In contrast, MAP (−4.67 mmHg; $n = 18$; $p = 0.014$) and, consequently, CPP (−4.21 mmHg; $n = 14$; $p = 0.013$) decreased significantly. Therefore, a significant increase in vasopressor dosage (norepinephrine +0.022 µg/kg/min; $n = 19$; $p = 0.039$) was necessary in order to compensate for the decrease in MAP and CPP. In none of the patients a critical CPP of <60 mmHg was observed (minimum 61 mmHg). In the short-term analysis, which includes the means of hourly values from 6 h to 1 h before and 1 h to 6 h after initiation of volatile sedation, CPP and MAP rose compared with values measured at the time point -1 h (Table 2 and Figure 1) indicating hemodynamic stabilization. However, this was achieved by keeping the norepinephrine dosages significantly increased compared with the pre-isoflurane baseline. ICP did not significantly change in the short-term analysis, although there was a slight mean increase (6 h to 1 h before versus +1 h to +6 h after start of isoflurane +0.34 mmHg; $n = 36$; $p = 0.443$). Consistent with the hypothesis that additional volatile sedation would result in a deeper sedation level BIS monitoring showed significantly decreased values after isoflurane was established (−15.16; $n = 16$; $p = 0.005$; −6 h to −1 h before versus +1 h to +6 h after isoflurane).

3.3. Mid- and long-term changes

In mid-term (−24 h to −1 h vs. +1 h to +24 h; Table 3) and long-term analysis (−48 h to −1 h vs. +1 to +144 h; Figure 2 and Table 4), a non-significant increase in ICP (mid-term: +0.60 mmHg, $n = 36$, $p = 0.057$; long-term: +0.65 mmHg, $n = 36$, $p = 0.055$) was observed. In the period from +1 h to +24 h after initiation of the ACD patients needed a significantly higher ventilator minute volume (+1.64 L/min; $n = 33$; $p < 0.001$), an increased peak inspiratory pressure (+2.26 cmH_2O; $n = 33$; $p < 0.001$) and PEEP (+0.45 cmH_2O; $n = 33$; $p = 0.037$, max. 15 cmH_2O) to maintain an adequate $PaCO_2$ when compared with the 24 h period before initiation of isoflurane. Despite adjustment to more invasive ventilation settings, $PaCO_2$ increased significantly to a mean of 40.14 mmHg (+2.90 mmHg; $n = 36$; $p < 0.001$; −24 to -1 h vs. +1 to +24 h). An analysis of blood markers revealed significantly higher concentrations of liver serum parameters, markers of muscle cell damage, and serum urea in the long-term period before vs. after isoflurane sedation. Compared with the period before volatile sedation (−48 h to −1 h) patients received less intravenous propofol sedation after the addition of isoflurane without reaching a significant threshold (−51.03 mg/h; $n = 18$; $p = 0.077$).

3.4. Early termination of isoflurane/adverse reactions

In 9 out of 36 patients, isoflurane sedation was stopped prematurely due to potential adverse side effects even though

TABLE 2 Immediate and short term changes in intracranial pressure and systemic vital parameters before and after additional sedation with volatile isoflurane.

	Parameter	Before isoflurane (−1h)	After isofluran (+1h)	Difference	95% CI	*n*	*p*-value
Cerebral monitoring	ICP (mmHg)	10.23 (3.43)	10.52 (5.07)	0.29 (3.77)	−1.09 to 1.67	31	0.671
	CPP (mmHg)	81.29 (8.19)	77.07 (8.05)	−4.21 (5.45)	−7.36 to −1.07	14	0.013
	BIS (Index)	39.14 (15.81)	35.00 (15.98)	−4.14 (13.70)	−12.06 to 3.77	14	0.222
Cardiovascular system	HF (beats/min)	64.78 (9.89)	64.72 (12.69)	−0.06 (6.51)	−3.29 to 3.18	18	0.972
	MAP (mmHg)	92.78 (9.33)	88.11 (7.05)	−4.67 (8.23)	−8.76 to −0.58	18	0.014
	Temp (°C)	36.86 (0.77)	36.85 (0.69)	−0.006 (0.170)	−0.090 to 0.079	18	0.891
	Norepi. (μg/kg/min)	0.094 (0.078)	0.117 (0.094)	0.022 (0.043)	−0.002 to 0.043	19	0.039

	Parameter	Before isoflurane (−6h to −1h)	After isoflurane (+1 to+6h)	Difference	95% CI	*n*	*p*-value
Cerebral monitoring	ICP (mmHg)	9.33 (3.07)	9.66 (3.29)	0.34 (2.62)	−0.55 to 1.22	36	0.443
	CPP (mmHg)	82.40 (6.64)	80.20 (5.50)	−2.23 (5.49)	−4.96 to 0.50	18	0.103
	BIS (Index)	42.08 (15.05)	26.91 (12.13)	−15.16 (18.66)	−25.11 to −5.22	16	0.006
Cardiovascular system	HF (beats/min)	63.70 (10.91)	64.73 (12.75)	1.03 (6.32)	−2.02 to 4.08	19	0.487
	MAP (mmHg)	91.30 (6.63)	90.19 (5.30)	−1.10 (5.19)	−3.60 to 1.40	19	0.366
	Temp (°C)	36.96 (0.69)	36.76 (0.70)	−0.21 (0.59)	−0.49 to 0.08	19	0.166
	Norepi. (μg/kg/min)	0.085 (0.067)	0.115 (0.092)	0.030 (0.055)	0.003 to 0.056	19	0.029

ICP, intracranial pressure; CPP, cerebral perfusion pressure; BIS, bispectral index; HF, heart frequency; MAP, mean arterial pressure; Temp, body core temperature; Norepi., norepinephrine dose, 95% CI, 95% confidence interval of the mean; n, number of patients with available data. Data represents the means (±SD) of immediate (time points −1 h vs + 1 h, values documented at this time) and short-term (means of period -6 h to −1 h vs + 1 h to + 6 h), changes before and after additional sedation with volatile isoflurane.

increased administration of anesthetics was considered necessary to maintain adequate sedation depth. Mainly, those patients exhibited ICP increases (5 patients with a mean ICP of 27.20 ± 6.54 mmHg, maximum of 37 mmHg after a median of 30 h [IQR, 7.5 to 125.5] following isoflurane administration). In one patient, the volatile sedation was terminated after 10 min isoflurane initiation due to an ICP peak (25 mmHg). Of note, the patient in question received isoflurane at a later treatment stage (starting on day 11 in the NICU) without developing an acute increase of ICP in the following 5-day period. However, this patient displayed critically increased liver serum parameters (γ-GT 2239 U/L, AST 693 U/L, ALT 1075 U/L) and hence isoflurane administration was discontinued again. The second most common reason for premature termination of volatile sedation was respiratory hypercapnic insufficiency with elevated $PaCO_2$, which was not controllable by increasing ventilation parameters (4 patients, with a mean $PaCO_2$ 57.20 ± 7.57 mmHg after a median 26.5 h [IQR, 13.25 to 37.5]).

It is noteworthy that the subgroup of patients with prematurely terminated isoflurane, and in particular those experiencing an elevated $PaCO_2$, had a significantly higher peak inspiratory pressure, lower lung compliance, and showed a trend towards higher ventilator minute volume in the period -24 h to -1 h prior to the implementation of the ACD when compared with the patients with continued isoflurane sedation (Table 5, Supplementary Table S1). None of the investigated patients met the diagnostic criteria for malignant hyperthermia, newly developed renal impairment or other severe side effects except those listed above.

4. Discussion

In the present retrospective analysis, we present data from 36 patients with severe aneurysmal SAH who received continuous isoflurane application in addition to a standard intravenous sedation regime in order to achieve an adequately deep sedation. While we measured positive effects on sedation depth by means of significantly decreased BIS values, we did not detect significant increases in ICP neither in the short-, mid-, nor long-term analysis (up to +144 h) in the vast majority of patients. However, in 25% of the patients balanced isoflurane sedation was stopped due ICP elevation (median 30 h after ACD implementation), or a clinically meaningful increase of PaCO2 or liver enzymes. This raises significant concerns about the safety of balanced sedation in patients with lung diseases facing increased ventilation pressure settings and low lung compliance, as well as the effect on ICP, since one patient developed an ICP increase directly after initiation of isoflurane.

Two previous prospective studies found no clinically relevant ICP increase up to 12 h after switching from intravenous to isoflurane sedation in a heterogeneous cohort of patients with acute brain injury (24, 25). In addition, a recent case series of seven patients with SAH who underwent decompressive craniectomy reported a slight/non-significant decrease of ICP in a 12 h follow up when patients received mono-isoflurane sedation due to insufficient sedation depth (26). So far, no severe adverse events after isoflurane administration in SAH patients have been reported;

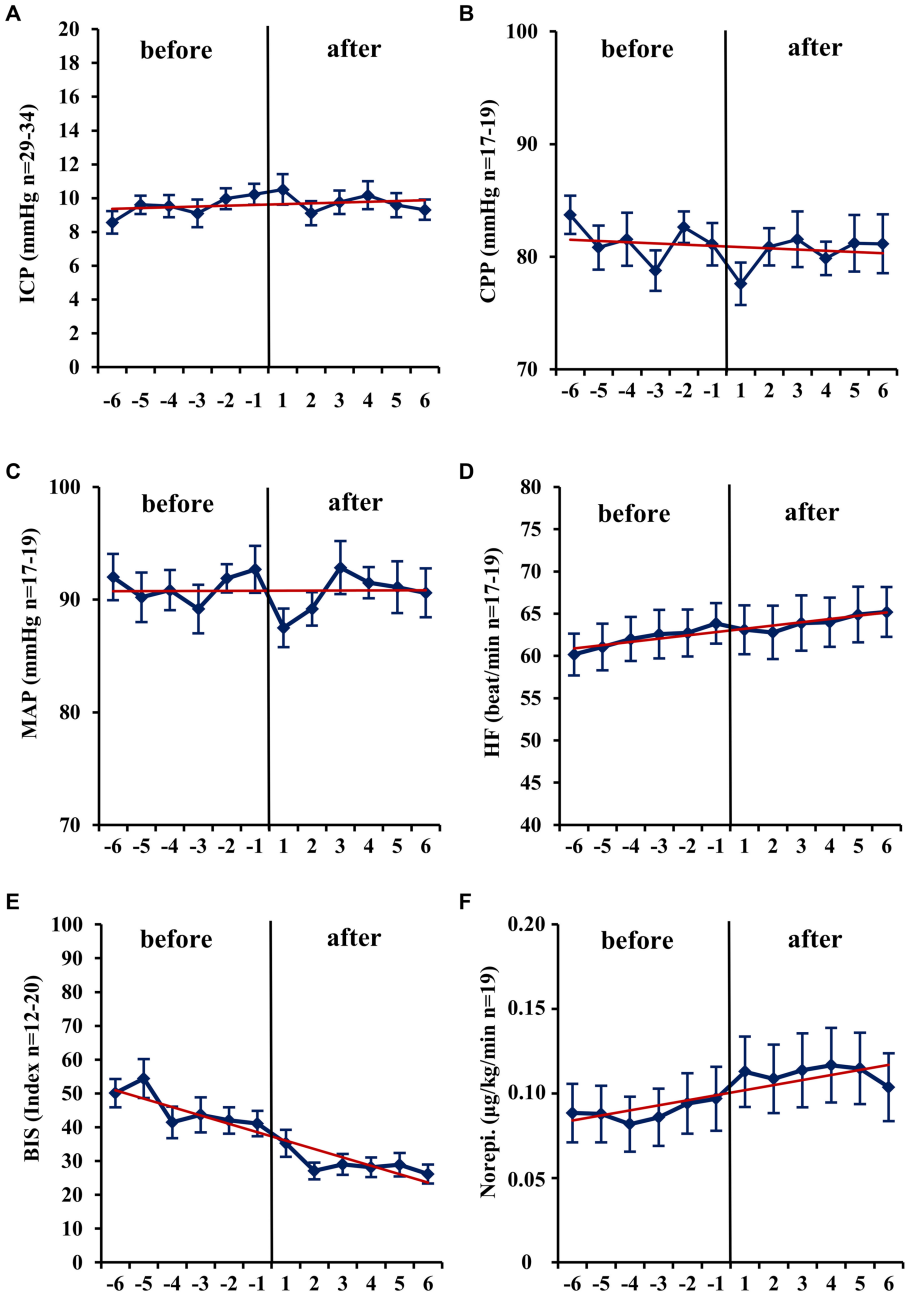

FIGURE 1
Short-term changes (– 6h to +6h) before and after administration of volatile isoflurane over time. ICP, intracranial pressure **(A)**; CPP, cerebral perfusion pressure **(B)**; MAP, mean arterial pressure **(C)**; HF, heart frequency **(D)**; BIS, bispectral index **(E)**; Norepi., Norephinephrine dose **(F)**; n, number of patients with available data. Data represents the hourly means (–6h to +6h) of all patients with available data at that time. Error bars given are SEM, standard error of the mean. The trend line shown is calculated as linear regression.

however, no study investigated long-term effects of volatile sedation with isoflurane in SAH patients beyond 12 h after isoflurane initiation.

In our series isoflurane was discontinued due to ICP increases (> 5 min) in five cases. While these ICP increases occurred mostly in the later course of treatment after a median of 30 h of ACD implementation, one patient developed an ICP elevation directly, within 10 min, after isoflurane was started. Noteworthy, episodic intracranial hypertension is a quite common phenomenon in the course of severe SAH as it is estimated that 50% of the patients experience ICP increases above 20 mmHg in acute (24 h), subacute (up to 7–10 days) and delayed stages after hemorrhage (33, 34). Therefore, the 11.1% of patients with documented episodes of increased ICP are in line with these findings. However, due to the lack of a control group, we cannot exclude a direct causal effect of low-dose isoflurane administration on ICP. Therefore, the use of balanced volatile sedation should be mitigated to SAH patients with an inadequate level of sedation using standard sedatives, and exclude patients with previous episodes of intracranial hypertension.

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TABLE 3 Mid-term changes (– 24h to +24h) before and after administration of volatile isoflurane.

	Parameter	Before isoflurane (–24h to –1h)	After isoflurane (+1h to+24h)	Difference	95% CI	*n*	*p*-value
Cerebral monitoring	ICP (mmHg)	9.34 (2.61)	9.95 (2.44)	0.60 (1.84)	−0.02 to 1.23	36	0.057
	CPP (mmHg)	81.61 (5.63)	80.56 (6.35)	−1.05 (5.12)	−3.08 to 0.97	27	0.295
	BIS (Index)	41.63 (12.76)	26.11 (12.61)	−15.52 (12.41)	−21.17 to −9.87	21	<0.001
Cardiovascular system	HF (beats/min)	63.56 (11.37)	64.90 (10.19)	1.34 (5.30)	−1.22 to 3.89	19	0.287
	MAP (mmHg)	91.62 (5.59)	90.77 (6.83)	−0.85 (4.37)	−2.95 to 1.26	19	0.410
	Temp (°C)	36.72 (0.62)	36.74 (0.50)	0.02 (0.48)	−0.21 to 0.25	19	0.847
Respiratory function	$SaO_{2\,(\%)}$	98.06 (1.39)	97.67 (1.20)	−0.39 (0.98)	−0.86 to 0.08	19	0.102
	FiO_2	38.08 (7.09)	40.93 (8.89)	2.86 (6.28)	0.70 to 5.01	35	0.032
	RMV (L/min)	8.66 (2.14)	10.29 (1.85)	1.64 (1.33)	1.17 to 2.12	33	<0.001
	Compliance	55.97 (12.68)	56.51 (13.25)	0.54 (7.08)	−1.97 to 3.05	33	0.905
	maxP (cmH_2O)	20.90 (4.36)	23.16 (3.83)	2.26 (2.12)	1.51 to 3.01	33	<0.001
	PEEP (cmH_2O)	8.14 (1.88)	8.59 (1.73)	0.45 (1.22)	0.02 to 0.88	33	0.037
	Horowitz index	288.10 (73.27)	274.70 (83.13)	−13.43 (43.32)	−28.31 to 1.46	35	0.076
	paO2 (mmHg)	105.60 (17.06)	105.60 (16.21)	−0.09 (18.65)	−6.41 to 6.21	36	0.786
Acid–base homeostasis	pH	7.43 (0.04)	7.43 (0.04)	−0.005 (0.04)	−0.02 to 0.01	36	0.509
	paCO2 (mmHg)	37.24 (2.64)	40.15 (3.29)	2.90 (4.28)	1.47 to 4.36	36	<0.001
	HCO_3^- (mmol/L)	24.93 (1.83)	26.04 (1.96)	1.11 (1.63)	0.56 to 1.66	36	<0.001
	Lactate (mmol/L)	1.40 (0.69)	1.41 (0.57)	0.01 (0.53)	−0.17 to 0.19	36	0.913
Drugs	Isoflurane (mL/h)	0 (0)	2.61 (0.91)	2.61 (0.91)	2.14 to 3.08	17	<0.001
	Ketamine (mg/h)	103.40 (85.45)	129.30 (77.24)	25.83 (60.39)	−5.21 to 56.88	17	0.097
	Midazolam (mg/h)	21.29 (20.39)	23.79 (19.32)	2.51 (12.49)	−3.92 to 8.93	17	0.600
	Nimodipin (mg/h)	0.74 (0.64)	0.71 (0.74)	−0.03 (0.62)	−0.35 to 0.29	17	0.847
	Norepi. (µg/kg/min)	0.084 (0.062)	0.118 (0.086)	0.034 (0.059)	0.005 to 0.062	19	0.024
	Sufentanil (µg/h)	35.44 (20.78)	30.63 (16.53)	−4.81 (15.73)	−13.52 to 3.91	15	0.194
	Propofol (mg/h)	72.00 (128.2)	27.63 (40.63)	−44.36 (123.2)	−107.70 to 18.99	17	0.432
Serum parameters	ALP (U/L)	186.10 (193.6)	203.90 (184.2)	17.79 (53.04)	−17.84 to 53.42	11	0.292
	Bilirubine (mg/dL)	0.43 (0.16)	0.38 (0.16)	−0.05 (0.13)	−0.106 to 0.010	23	0.102
	CK (U/)l	324.80 (448.2)	428.00 (520.4)	103.30 (256.2)	−110.9 to 317.4	8	0.641
	CRP (mg/dL)	5.43 (4.09)	5.59 (3.61)	0.16 (2.96)	−0.84 to 1.16	36	0.945
	GGT (U/L)	271.30 (449.4)	311.10 (452.9)	39.79 (138.7)	−9.38 to 88.96	33	0.003
	ALT (U/L)	55.46 (65.44)	53.79 (62.93)	−1.68 (37.81)	−16.34 to 12.98	28	0.933
	AST (U/L)	65.06 (96.22)	67.94 (85.5)	2.88 (33.52)	−9.01 to 14.76	33	0.453
	Urea (mg/dL)	29.68 (13.62)	33.62 (15.91)	3.93 (6.02)	1.87 to 6.00	35	<0.001
	IL-6 (pg/dL)	30.29 (26.73)	23.31 (16.97)	−6.98 (22.93)	−14.74 to 0.78	36	0.105
	Creatinine (mg/dL)	0.82 (0.22)	0.84 (0.25)	0.03 (0.08)	−0.002 to 0.054	35	0.090
	Myoglobine (mg/dL)	125.80 (147.80)	258.90 (465.4)	133.10 (407.90)	−16.56 to 282.70	31	0.490

ICP, intracranial pressure; CPP, cerebral perfusion pressure; BIS, bispectral index; HF, heart frequency; MAP, mean arterial pressure; Temp, body core temperature; SaO_2, peripheral oxygen saturation; FiO_2, fraction of inspired oxygen; RMV, respiratory minute volume; maxP, peak inspiratory pressure; PEEP, post-end-expiratory pressure, Horowitz index, PaO_2/FiO_2; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; pH, blood pH in blood gas analysis; HCO_{3-}, standard bicarbonate; Norepi., norepinephrine dose; Serum parameters: ALP, alkaline phosphatase; CK, creatine kinase; CRP, C-reactive protein; GGT, gamma glutamyl transpeptidase; AST, aspartate transaminase; ALT, alanine transaminase; IL-6, interleukin 6; 95% CI, 95% confidence interval of the mean; n, number of patients with available data. Data represent means (±SD) or median (IQR) of all values given in the period (−24 h to −1 h vs + 1 h to + 24 h) before and after additional sedation with volatile isoflurane.

In contrast to our study, Purrucker et al. demonstrated a significant increase in ICP in the first hour after a complete switch from intravenous narcotics to sevoflurane in 25 patients with acute brain injury (21). In their study, ICP crisis that occurred in five patients was potentially attributed to a significant decrease in MAP and CPP caused by the vasodilatory effects of sevoflurane or an increase in $PaCO_2$. Of

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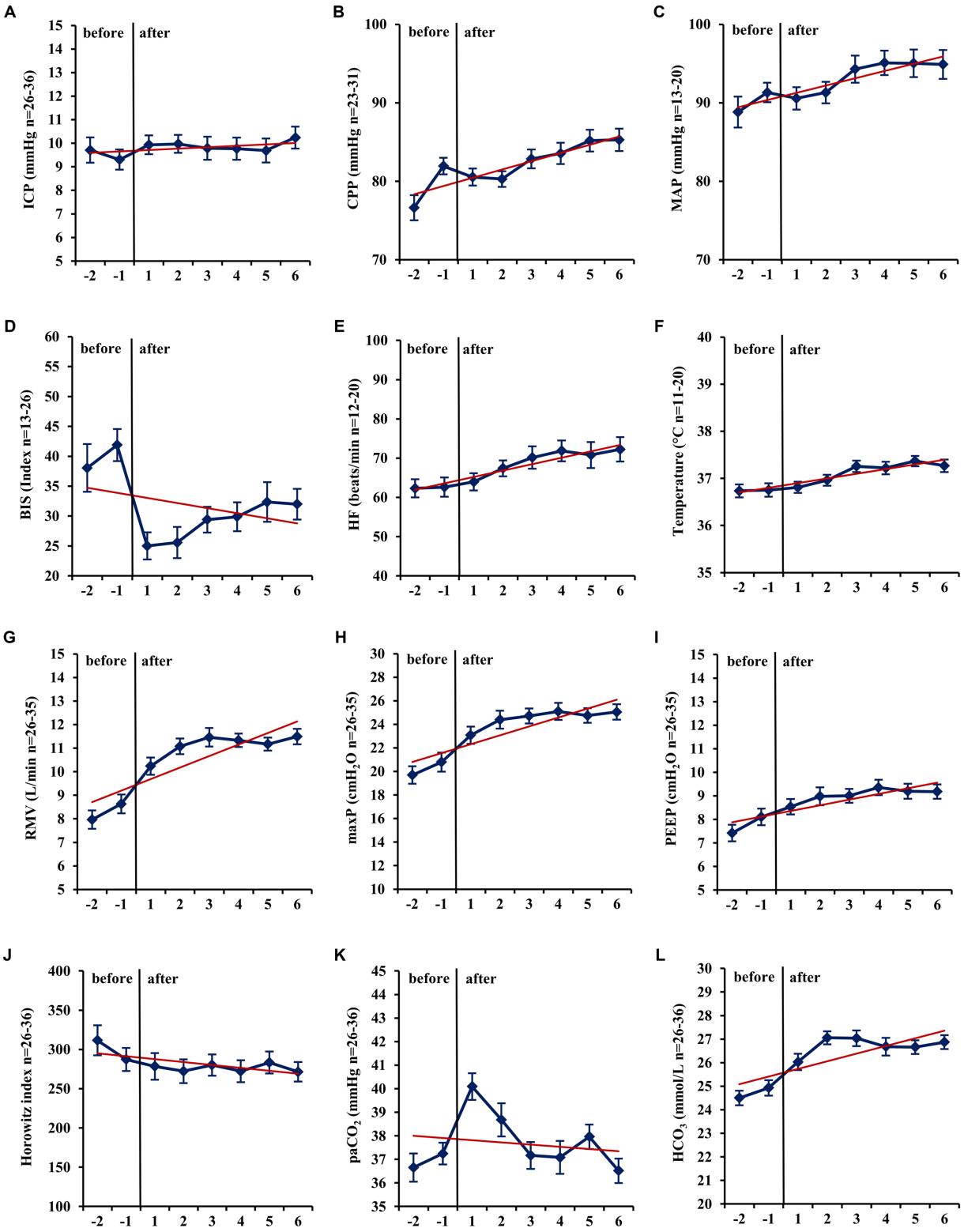

FIGURE 2
Long-term changes before and after administration of volatile isoflurane over time (−2days to +6days). ICP, intracranial pressure **(A)**; CPP, cerebral perfusion pressure **(B)**; MAP, mean arterial pressure **(C)**; BIS, bispectral index **(D)**; HF, heart frequency **(E)**; Temp, body core temperature **(F)**; RMV, respiratory minute volume **(G)**; maxP, peak inspiratory pressure **(H)**; PEEP, post endexpiratory pressure **(I)**; Horowitz index, PaO_2/FiO_2, PaO_2, arterial partial pressure of oxygen **(J)**; $PaCO_2$, arterial partial pressure of carbon dioxide **(K)**; HCO_{3-}, standard bicarbonate **(L)**; *n*, number of patients with available data. Data represent the daily means (−2 days to +6 days) of all patients with available data at that time. The error bars represent the SEM, standard error of the mean. The trend line shown was calculated using linear regression.

TABLE 4 Long-term changes (− 48h to +144h) before and after administration of volatile isoflurane.

	Parameter	Before isoflurane (−48h to −1h)	After isoflurane (+1h to+144h)	Difference	95% CI	*n*	*p*-value
Cerebral monitoring	ICP (mmHg)	9.48 (2.49)	10.13 (2.15)	0.65 (1.98)	−0.02 to 1.32	36	0.055
	CPP (mmHg)	79.29 (7.10)	81.95 (7.13)	2.67 (6.97)	−0.69 to 6.03	19	0.196
	BIS (Index)	41.63 (15.54)	24.76 (10.29)	−16.87 (14.33)	−26.50 to −7.24	11	<0.001
Cardiovascular system	HF (beats/min)	64.06 (10.99)	68.48 (10.02)	4.42 (5.67)	1.69 to 7.15	19	0.003
	MAP (mmHg)	90.25 (6.38)	92.77 (7.26)	2.51 (5.43)	−0.10 to 5.13	19	0.096
	Temp (°C)	36.68 (0.55)	36.96 (0.49)	0.28 (0.39)	0.09 to 0.48	19	0.005
Respiratory function	$SaO_{2\,(\%)}$	98.03 (1.26)	97.98 (0.73)	−0.04 (1.19)	−0.61 to 0.53	19	0.145
	FiO_2	38.07 (7.25)	41.51 (8.27)	3.44 (7.46)	0.89 to 6.01	35	0.015
	RMV (L/min)	8.31 (2.03)	11.01 (1.58)	2.71 (1.36)	2.22 to 3.19	33	<0.001
	Compliance	56.62 (12.60)	55.70 (11.51)	−0.92 (7.15)	−3.45 to 1.62	33	0.469
	maxP (cmH_2O)	20.31 (4.03)	24.43 (3.37)	4.14 (2.79)	3.14 to 5.13	33	<0.001
	PEEP (cmH_2O)	7.81 (1.78)	8.88 (1.61)	1.07 (1.52)	0.53 to 1.61	33	<0.001
	Horowitz index	302.00 (84.17)	282.80 (65.4)	−19.19 (47.93)	−37.42 to −0.96	29	0.040
	paO2 (mmHg)	110.60 (18.92)	107.30 (12.81)	−3.34 (18.1)	−9.47 to 2.78	36	0.276
Acid–base homeostasis	pH	7.426 (0.033)	7.451 (0.026)	0.025 (0.040)	0.011 to 0.038	36	<0.001
	paCO2 (mmHg)	37.14 (2.56)	38.37 (2.74)	1.23 (3.44)	0.07 to 2.40	36	0.039
	HCO_3^- (mmol/L)	24.61 (1.56)	26.67 (1.30)	2.06 (1.87)	1.43 to 2.69	36	<0.001
	Lactate (mmol/L)	1.39 (0.67)	1.17 (0.30)	−0.22 (0.54)	−0.40 to −0.03	36	0.022
Drugs	Isoflurane (mL/h)	0.00 (0.)	2.74 (0.71)	2.74 (0.71)	2.39 to 3.09	18	<0.001
	Ketamine (mg/h)	90.03 (85.83)	117.90 (59.49)	27.876 (79.71)	−11.77 to 67.51	18	0.156
	Midazolam (mg/h)	18.07 (18.62)	18.59 (14.73)	0.52 (14.43)	−6.66 to 7.70	18	0.881
	Nimodipin (mg/h)	0.66 (0.59)	0.75 (0.64)	0.10 (0.75)	−0.28 to 0.47	18	0.596
	Norepi. (μg/kg/min)	0.084 (0.061)	0.098 (0.060)	0.014 (0.047)	−0.009 to 0.036	18	0.220
	Sufentanil (μg/h)	34.27 (18.00)	23.69 (14.48)	−10.58 (16.15)	−18.61 to −2.55	18	0.002
	Propofol (mg/h)	72.36 (103.4)	21.33 (36.19)	−51.03 (104.40)	−103 to 0.90	18	0.077
Serum parameters	ALP (U/L)	107.40 (105.6)	163.80 (151.3)	56.44 (72.13)	23.60 to 89.27	21	<0.001
	Bilirubine (mg/dL)	0.55 (0.27)	0.45 (0.16)	−0.10 (0.25)	−0.20 to 0.004	25	0.057
	CK (U/L)	182.20 (264.3)	257.80 (326.3)	75.61 (264.7)	−48.26 to 199.5	20	0.047
	CRP (mg/dL)	4.70 (3.92)	7.61 (4.64)	2.91 (6.08)	0.75 to 5.07	33	0.005
	GGT (U/L)	104.70 (157.4)	312.50 (404.9)	207.80 (304.5)	91.95 to 323.60	29	<0.001
	ALT (U/L)	36.19 (25.12)	59.68 (54.98)	23.49 (45.61)	6.46 to 40.52	30	0.004
	AST (U/L)	37.21 (27.89)	65.90 (68.67)	28.69 (53.22)	9.51 to 47.88	32	<0.001
	Urea (mg/dL)	28.53 (10.92)	44.88 (17.08)	16.35 (16.67)	10.63 to 22.08	35	<0.001
	IL-6 (pg/dL)	27.58 (20.07)	53.28 (55.10)	25.70 (61.88)	4.44 to 46.96	35	0.011
	Creatinine (mg/dL)	0.81 (0.21)	0.85 (0.27)	0.03 (0.13)	−0.01 to 0.07	35	0.211
	Myoglobine (mg/dL)	110.50 (141.2)	282.80 (294.4)	172.30 (225.0)	88.30 to 256.30	30	<0.001

ICP, intracranial pressure; CPP, cerebral perfusion pressure; BIS, bispectral index; HF, heart frequency; MAP, mean arterial pressure; Temp, body core temperature; SaO_2, peripheral oxygen saturation; FiO_2, fraction of inspired oxygen; RMV, respiratory minute volume; maxP, peak inspiratory pressure; PEEP, post-end-expiratory pressure, Horowitz index, PaO_2/FiO_2; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; pH, blood pH in blood gas analysis; HCO_{3-}, standard bicarbonate; Norepi., norepinephrine dose; Serum parameters: ALP, alkaline phosphatase; CK, creatine kinase; CRP, C-reactive protein; GGT, gamma glutamyl transpeptidase; AST, aspartate transaminase; ALT, alanine transaminase; IL-6, interleukin 6; 95% CI, 95% confidence interval of the mean; n, number of patients with available data. Data represent means (±SD) or median (IQR) of all values given in the period (−48 h to −1 h vs + 1 h to + 144 h) before and after additional sedation with volatile isoflurane.

note, in their study, two patients who exhibited ICP increases were switched from volatile sedation with sevoflurane to isoflurane instead and remained stable regarding their ICP thereafter.

In order to avoid hemodynamic instability, we focused on a balanced sedation regiment combining common intravenous sedatives with inhaled isoflurane at a lower concentration (MAC 0.18–0.5 for a

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TABLE 5 Comparison of baseline parameters between patients who tolerated volatile sedation and patients with premature termination of volatile sedation.

	Parameter	Continued volatile sedation *n* =11–27 (–24h to –1h)	Discontinued volatile sedation *n* =5–9 (–24h to –1h)	Difference	*p*-value
Baseline parameters	Age (years)	56.04 (11.00)	53.78 (7.00)	−2.26 (3.93)	0.673
	Sex (m/f)	7/20 (26/74%)	3/6 (33/66%)	–	–
	Duration (hours)	288 [120 to 408]	30 [12.5 to 67.5]	−258	<0.001
	Fisher scale	4 [3 to 4]	4 [4 to 4]	0	>0.999
	WFNS score	4 [2 to 5]	4 [3.5 to 5]	0	>0.999
Cerebral monitoring	ICP (mmHg)	9.42 (2.78)	9.11 (2.15)	−0.31 (1.02)	0.759
	CPP (mmHg)	80.69 (5.85)	84.22 (4.28)	3.53 (2.42)	0.158
	BIS (Index)	41.01 (9.11)	44.27 (25.14)	3.25 (7.24)	0.658
Cardiovascular system	HF (beats/min)	64.03 (12.48)	62.25 (8.54)	−1.78 (6.08)	0.964
	MAP (mmHg)	90.74 (5.65)	94.07 (5.15)	3.32 (2.89)	0.265
	Temp (°C)	36.90 (0.49)	36.22 (0.75)	−0.68 (0.29)	0.032
Respiratory function	SaO_2 (%)	97.83 (1.45)	98.70 (1.10)	0.87 (0.72)	0.239
	FiO_2	37.60 (6.92)	39.46 (7.81)	1.85 (2.76)	0.507
	RMV (L/min)	8.30 (1.5)	9.76 (3.37)	1.45 (0.84)	0.094
	Compliance	58.46 (11.99)	48.20 (12.3)	−10.25 (4.90)	0.045
	maxP (cmH_2O)	19.80 (3.76)	24.32 (4.56)	4.52 (1.61)	0.009
	PEEP (cmH_2O)	8.02 (1.92)	8.49 (1.79)	0.47 (0.77)	0.545
	Horowitz index	284.17 (73.74)	299.54 (75.00)	15.37 (28.6)	0.595
	paO_2 (mmHg)	103.66 (17.41)	111.59 (15.34)	7.41 (6.52)	0.231
Acid–base homeostasis	pH	7.42 (0.03)	7.45 (0.04)	0.03 (0.014)	0.034
	$paCO_2$ (mmHg)	37.66 (2.24)	35.97 (3.42)	−1.69 (0.99)	0.097
	HCO_3^- (mmol/L)	24.73 (1.82)	25.54 (1.82)	0.81 (0.70)	0.254
	Lactate (mmol/L)	1.40 (0.73)	1.39 (0.60)	−0.01 (0.27)	0.823
Drugs	Ketamine (mg/h)	94.64 (90.39)	132.03 (69.5)	37.39 (49.50)	0.462
	Midazolam (mg/h)	17.17 (20.19)	34.67 (16.58)	17.50 (11.20)	0.144
	Nimodipin (mg/h)	0.84 (0.6)	0.41 (0.72)	−0.43 (0.36)	0.345
	Norepi. (µg/kg/min)	0.081 (0.069)	0.092 (0.042)	0.012 (0.033)	0.500
	Sufentanil (µg/h)	34.32 (23.81)	38.49 (10.38)	0.41 (12.5)	0.745
	Propofol (mg/h)	86.42 (142.58)	25.10 (50.21)	−61.32 (74.0)	0.336

M, male; f, female; duration, duration of volatile sedation; SAH, subarachnoid hemorrhage; Fisher Grade; WFNS grade, World Federation of Neurological Surgeons; ICP, intracranial pressure; CPP, cerebral perfusion pressure; BIS, bispectral index; HF, heart frequency; MAP, mean arterial pressure; Temp, body core temperature; SaO2, peripheral oxygen saturation; FiO2, fraction of inspired oxygen; RMV, respiratory minute volume; maxP, peak inspiratory pressure; PEEP, post endexpiratory pressure, Horowitz index, PaO_2/FiO_2; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; pH, blood pH in blood gas analysis; HCO3-, standard bicarbonate; Norepi., norepinephrine dose; n, number of patients with available data. Data represent means (±SD) or median (IQR) of all values given in the period (−24 h to −1 h before start of isoflurane).

40-year-old standard patient) compared with the previous studies that targeted a MAC of ≥0.5. As expected, the addition of isoflurane sedation with intravenous hypnotic agents resulted in more adequate sedation depth measured with bispectral index. BIS correlates with common sedation scales such as RAAS and has already been reported to be useful for the differentiation of adequate from inadequate sedation depth in critically ill patients amongst others with SAH (35–38). As an additional advantage propofol dosage, which often is deemed indispensable in intravenous sedation protocols, could be reduced or even replaced by addition of isoflurane, thereby diminishing the imminent risk of propofol infusion syndrome (PRIS) (39).

Although our data also revealed a decrease in MAP and CPP in the first hour after initiation of isoflurane, none of the patients in our study dropped below the critical threshold of a CPP < 60 mmHg. After this short-term adaptation in blood pressure via increased norepinephrine dosage, the cardiovascular parameters remained stable in all patients until the end of isoflurane administration. These findings might favor a balanced sedation protocol over a complete switch to sevoflurane sedation in terms of hemodynamic stability, even though isoflurane is known for its more pronounced vasodilatory effect (40, 41).

Regarding the potential adverse effects of long-term isoflurane administration on extracerebral organ function, patients showed an

increase in liver serum parameters, markers of muscle cell damage, and serum urea in long-term analysis. In one patient with a severe increase in serum liver enzyme concentrations, sedation with isoflurane was discontinued. However, other reasons for elevated serum parameters including liver enzymes, myoglobin and creatine kinase are possible and common, such as the SAH itself, toxicity by other drugs, systemic infections or the administration of parenteral nutrition (42–44). As isoflurane is a stable molecule only 0.2% is metabolized by the liver, and thus far, no clinical human studies have demonstrated hepatotoxicity or nephrotoxicity of low-dose volatile sedation in ICUs (43, 45, 46). Nevertheless, we cannot exclude a direct effect of volatile sedation with isoflurane on liver function in our cohort. Hence, patients with preexisting liver disease must be monitored with caution, when balanced sedation with isoflurane is in place. However, it needs to be considered that intravenous sedatives often exhibit detrimental liver toxicity, especially when administered in the inevitable high doses used in our cohort in order to reach sufficient sedation depth.

As already evidenced in previous studies, we observed a significant increase in $PaCO_2$ on the first day after the implementation of the ACD. This might be attributed to an increased dead space in the ventilator system or the result of a known isoflurane-dependent increase in intrapulmonary shunt (47, 48). In the majority of patients, this increase in $PaCO_2$ could be counteracted by a significant increase in respiratory minute volume. However, isoflurane was discontinued in four patients due to uncontrollable hypercapnia. Data from our baseline comparison between patients with and without premature termination of isoflurane revealed that a pre-existing high peak inspiratory pressure > 20 cmH_2O and a low lung compliance might serve as a predictor of pulmonary adverse events during isoflurane treatment. Although recent developments show a trend towards volatile vaporizers with lower dead space, volatile sedation in patients with SAH should be limited to patients without lung diseases and low ventilation pressure settings (49).

While providing new data specifically describing possible advantages of a balanced anesthesia protocol over mono-inhalational sedation, our study also has several limitations. First of all, it needs to be considered that establishing this balanced sedation protocol may not be feasible for all NICUs depending on the experience of the treating physicians with volatile anesthetic agents. Due to its retrospective nature, no confirmatory analysis was performed, and all *value of p*s are descriptive only. We did not include secondary outcome parameters other than death on NICU, since their interpretation would be misleading for several reasons: First, SAH patients in our NICU were often transferred into specialized neuro-rehabilitation and weaning centers for continuation of their intensive care treatment. Secondly, only relatively stable patients were considered to profit from balanced isoflurane sedation causing important selection bias. Isoflurane treatment was initiated after the individual decision of the treating physician; therefore, it was administered at different times after the onset of the hemorrhage. As SAH pathomechanisms vary over time, the current setup does not allow for speculation as to which component of SAH pathology is primarily influenced by isoflurane. Since there is no control group without isoflurane administration and due to the limited sample size, it is impossible to investigate whether outcome measures may be influenced by isoflurane treatment or to draw a conclusion regarding the safety of isoflurane treatment in these patients; however, our data help to better characterize the feasibility of long-term isoflurane sedation in patients with SAH. Hence, prospective studies investigating the safety of balanced volatile sedation in critically ill SAH patients are needed. Moreover, potentially favorable side effects on SAH in terms of putative neuroprotective effects versus its potential hazardous side effects can be elucidated.

In summary, a balanced sedation protocol including low-dose inhalational isoflurane via the Sedaconda® ACD can achieve adequate sedation levels in some critically ill SAH patients. However, therapy had to be withdrawn in a substantial amount of patients mostly due to hypercapnia or ICP increase. Especially in patients with pre-existing lung injury, hemodynamic instability, and previous intracranial hypertension the balanced sedation protocol bears the risk of these adverse events. Therefore, the question if it is safe to use isoflurane in critically ill SAH patients remains unsolved and must consequently be addressed in a randomized trial.

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 Ethical Committee of the Faculty of Medicine, LMU Munich, Pettenkoferstrasse 8a, 80336 Munich, Germany. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

MBM designed the study, analyzed and interpreted data and wrote the manuscript. NAT, SMS interpreted data, provided resources and revised the manuscript. JB critically edited the manuscript. VH designed the study, interpreted data, wrote the manuscript and supervised the study. All authors contributed to the article and approved the submitted version.

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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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1164860/full#supplementary-material

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Association between baseline pulse pressure and hospital mortality in non-traumatic subarachnoid hemorrhage patients: a retrospective cohort study

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Background and purpose: Previous studies have described an association between pulse pressure (PP) level and mortality in stroke patients. Evidence of associations between PP level and the risk of mortality remains unknown in non-traumatic subarachnoid hemorrhage (SAH) patients. We aimed to explore the relationship between the baseline PP level and hospital mortality.

Methods: This cohort study of 693 non-traumatic SAH adults used Medical Information Mart for Intensive Care (MIMIC-IV) data from 2008–2019 admissions to Intensive Care Unit (ICU). PP level was calculated as the first value after admission to the ICU. The endpoint of the study was in-hospital mortality. Cox proportional hazards models were utilized to analyze the association between baseline PP level and hospital mortality. Restricted Cubic Splines (RCS) analysis was utilized to determine the relationship curve between hospital mortality and PP level and examine the threshold saturation effect. We further applied Kaplan–Meier survival curve analysis to examine the consistency of these correlations. The interaction test was used to identify subgroups with differences.

Results: The mean age of the study population was 58.8±14.6years, and 304 (43.9%) of participants were female. When baseline PP level was assessed in quartiles, compared to the reference group (Q1≤56mmHg), the adjusted hazard ratio (HR) in Q2 (57–68mmHg), Q3(69–82mmHg), Q4 (≥83mmHg) were 0.55 (95% CI: 0.33–0.93, p=0.026), 0.99 (95% CI, 0.62–1.59, p=0.966), and 0.99 (95% CI: 0.62–1.59, p=0.954), respectively. In the threshold analysis, for every 5mmHg increase in PP level, there was an 18.2% decrease in hospital mortality (adjusted HR, 0.818; 95% CI, 0.738–0.907; p=0.0001) in those with PP level less than 60mmHg, and a 7.7% increase in hospital mortality (adjusted HR, 1.077; 95% CI, 1.018–1.139; p=0.0096) in those with PP level was 60mmHg or higher.

Conclusion: For patients with non-traumatic SAH, the association between baseline PP and risk of hospital mortality was non-linear, with an inflection point at 60mmHg and a minimal risk at 57 to 68mmHg (Q2) of baseline PP level.

KEYWORDS

pulse pressure, non-traumatic subarachnoid hemorrhage, hospital mortality, retrospective, MIMIC

Introduction

Despite advances in critical care, non-traumatic subarachnoid hemorrhage (SAH) remains a devastating form of stroke with a high mortality rate (1). It is estimated that up to 40% of non-traumatic SAH patients die in the hospital (2). Given the mortality risk of subarachnoid hemorrhage, it highlights the critical need for non-invasive and inexpensive tests to help identify patients at increased risk for mortality and further optimize the treatment.

Among the various factors identified that may increase the mortality risk of non-traumatic SAH, blood pressure (BP) is one of the most important, as it is essential for maintaining adequate cerebral perfusion pressure (3, 4). In addition to the systolic and diastolic stable components, BP is well characterized by its pulsatile nature and is estimated by pulse pressure (PP), which can either become broader or narrower. The main determinants of PP are per-pulse output and aortic resistance. It is inversely related to elastic properties of arterial wall, i.e., higher the PP level, stiffer the large arterial wall, which is reduces aortic compliance (5). PP also reflects fluid responsiveness, stroke, and left ventricular function and volume. Notably, a recent systematic review and meta-analysis of 11 studies revealed that a high PP level was associated with an increased risk of stroke (6); Furthermore, there is mounting evidence that PP level was strongly related to mortality in patients with acute intracerebral hemorrhage and ischemic stroke, as well as increasing stroke recurrence (5, 7–12). A previous study including 156 patients with SAH demonstrated no statistically significant association between admission PP and hospital mortality (13). However, evidence of associations between PP level and the risk of mortality remains unknown in non-traumatic subarachnoid hemorrhage (SAH) patients.

The Medical Information Mart for Intensive Care (MIMIC-IV) database of ICU allowed us to assess the associations of baseline PP level with non-traumatic SAH. We aimed to explore the association between baseline PP level and hospital mortality.

Materials and methods

Data source

The MIMIC-IV maintains a standardized and publicly accessible ICU database, an extensive single-center database, which includes 50,048 ICU admissions at Boston's Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2019. To extract data, all authors completed the National Institutes of Health's web-based course "Protecting Human Research Participants" (certification number: 46264188) and obtained authorization to access the database. The study was carried out following the Helsinki Declaration guidelines and was reviewed and approved by the Massachusetts Institute of Technology and the Institutional Review Board of Beth Israel Deaconess Medical Center (BIDMC, Boston, MA, United States). All data were de-identified to protect patient privacy, and the need for informed consent was waived. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (14).

Study population

We conducted a retrospective analysis of 693 non-traumatic SAH database from an online international database from 2008 to 2019, the Medical Information Mart for Intensive Care (MIMIC-IV) (15). Data includes demographics, clinical parameters, clinical laboratory tests, intervention, medical history, and medical data. Among them, 693 patients with non-traumatic SAH were selected based on the record of ICD-9 code 430, and ICD-10 codes I60, I600 to I6012, I6000 to I6002, I6020 to I6022, I6030 to I6032, I6050 to I6052. Patients who met the following criteria were included: (1) diagnosed as non-traumatic SAH at ICU admission; (2) aged ≥18 years; (3) had their first ICU admission. The exclusion criteria were as follows: (1) missing admission systolic blood pressure (SBP) or diastolic blood pressure (DBP) data from invasive measurements; (2) dying within 24 h of ICU admission. Finally, 693 patients (389 male and 304 female) were enrolled, and complete baseline data was collected.

Data extraction

All relevant variables were taken from the medical record using Structured Query Language (SQL) with PostgreSQL in the MIMIC-IV database. As previously stated, we accumulated the following patient characteristics: age (≥18 years), sex (389 male and 304 female), ethnicity (white, or others), SBP, DBP, heart rate, respiratory rate (RR), percutaneous oxygen saturation (SpO2), Glasgow Coma Scale (GCS) score, Charlson comorbidity index, comorbidities (including myocardial infarction, congestive heart failure, chronic pulmonary disease, diabetes, hypertension, paraplegia, and sepsis), white blood cell (WBC), platelet, hemoglobin, glucose, sodium, potassium, BUN, creatinine and therapies performed during the first day of ICU and hospital stay (including the use of norepinephrine, vasopressin, dopamine, nicardipine, nimodipine, embolization of aneurysm, and clipping of aneurysm). In addition, the ICD-9 discharge diagnostic codes were examined for the hypertension diagnosis.

Baseline PP level measurement and definition of outcomes

Baseline arterial blood pressure defined as the first measurement recorded on admission to the ICU. These values were invasively obtained through an arterial catheter. The pulse pressure (PP; first SBP minus first DBP) were calculated for each patient (16, 17). The

primary endpoint was all-cause hospital mortality, with secondary endpoints including 28 day post-admission and all-cause ICU mortality.

Statistical analyses

The means ± SD or median and interquartile ranges (IQR) were used to describe continuous variables. Numbers and percentages were used to represent categorical data. The difference between the admission PP level quartile was compared using one-way ANOVA for continuous data and chi-squared tests for categorical variables (18).

Next, we used cox proportional hazards models to investigate the relationship between PP level at baseline and hospital mortality. We performed three models. We adjusted for no covariates in the crude model. We adjusted for age, sex, and ethnicity in Model I. In the Model II, we adjusted for age, sex, ethnicity, RR, WBC, platelets, GCS score, Charlson Comorbidity Index, congestive heart failure, myocardial infarction, hypertension, sepsis, vasoactive drugs, nicardipine, nimodipine, and aneurysm embolization. The results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). We chose these confounders based on their relationship with the clinical outcomes of interest or significant changes in effect estimates of more than 10% (19).

Threshold analysis in the association of baseline PP level with hospital mortality was conducted with a two-piece-wise Cox regression model using restricted cubic spline analysis (RCS) (20, 21). The inflection point for the baseline PP level was identified using "exploratory" analyses, which involved moving the trial turning point along a pre-defined interval and selecting the one with the maximum model likelihood. A log-likelihood ratio test was also performed, and the one-line linear regression model was compared to the two-piece-wise linear model (20). We used the bootstrap resampling method to calculate the 95% CI for the turning point, as described in the previous analysis (21–23). The Kaplan–Meier method was used to estimate survival, and any differences in survival were assessed using stratified log-rank tests and bootstrap resampling method (20).

Furthermore, we also performed sensitivity analyses to confirm the stability of our study. Interactions and stratified analyses were conducted using sex (male vs. female), myocardial infarction (no vs. yes), congestive heart failure (no vs. yes), hypertension (no vs. yes), diabetes (no vs. yes), endovascular therapy of aneurysm (no vs. yes), and GCS (<8 and ≥8) results. Cox proportional hazards models were used to assess heterogeneity across subgroups, and likelihood ratio testing was used to examine interactions between subgroups and baseline PP level (18). We used the predicted mean matching method to replace missing values in the data for the missing dataset (24). Supplementary Table S1 displays the details of the missing data.

In all analyses, $p < 0.05$ (two-sided) was considered statistically significant. All data analyses were carried out using R 3.6.1[1] and the EmpowerStats package (www.empowerstats.com, X&Y solutions, Inc. Boston MA) (25, 26).

1 http://www.r-project.org

Results

Baseline characteristics

Our study included 693 non-traumatic SAH participants with complete SBP and DBP recorded through invasive measurements from the MIMIC-IV database (Figure 1). The mean age of the study participants was 58.8 ± 14.6 years, and 304 (43.9%) of participants were female. Table 1 describes the baseline characteristics of included patients through the quartiles of the baseline PP level (Q1 < 56 mmHg, 57 ≤ Q2 < 68 mmHg, 69 ≤ Q3 < 82 mmHg, Q4 ≥ 83 mmHg) in this study.

Participants with higher levels of PP tended to be older; more likely to have higher systolic blood pressure; comorbid with myocardial infarction, diabetes, sepsis; however participants with lower levels of PP more likely to have lower GCS; to be more likely use norepinephrine, vasopressin, and dopamine drugs. (All $p < 0.05$).

Association between baseline PP level and hospital mortality

The univariate analysis demonstrated that age, ethnicity, RR, myocardial infarction, congestive heart failure, Charlson comorbidity index, WBC, platelets, glucose, sodium, potassium, BUN, creatinine, norepinephrine, vasopressin, nicadipine, nimodipine, GCS and embolization of aneurysm were associated with hospital mortality (all $p < 0.05$) (Supplementary Table S2).

Multiple Cox proportional hazard regression analyses were used to investigate the relationship between baseline PP level and hospital mortality in Table 2. We performed three model. We adjusted for no covariates in the crude model. We adjusted for age, sex, and ethnicity in Model I. We adjusted for age, gender, ethnicity, RR, WBC, platelets, GCS score, Charlson Comorbidity Index, congestive heart failure, myocardial infarction, hypertension, sepsis, vasoactive drugs,

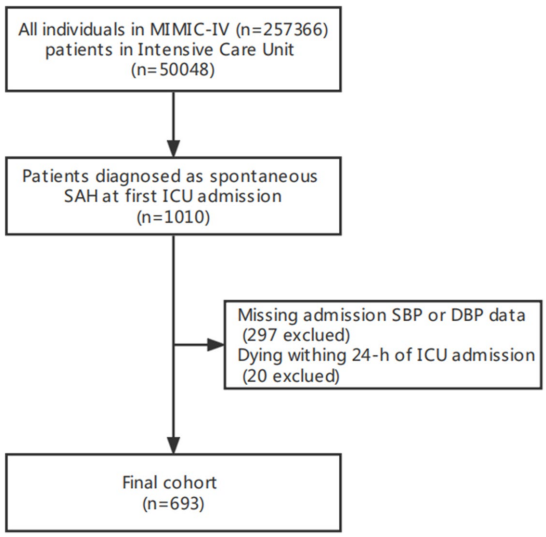

FIGURE 1
Flow chart of study population. MIMC-IV, medical information mart for intensive care IV; ICU, intensive care unit.

TABLE 1 Population characteristics by quartiles of baseline pulse pressure.

Variables	Pulse pressure (mmHg)					*p* value
	Total	Q1 (≤56)	Q2 (57–68)	Q3 (69–82)	Q4 (≥83)	
No of individuals	693	168	165	185	175	
Age, years	58.8 ± 14.6	54.7 ± 14.1	56.4 ± 13.5	60.0 ± 14.9	64.0 ± 14.0	<0.001
Female, *n*(%)	304 (43.9)	80 (47.6)	68 (41.2)	79 (42.7)	77 (44)	0.674
White race, *n*(%)	293 (42.3)	75 (44.6)	59 (35.8)	77 (41.6)	82 (46.9)	0.187
Vital signs						
SBP, mmHg	136.9 ± 24.7	110.4 ± 17.0	130.1 ± 13.3	142.1 ± 13.6	163.1 ± 18.6	<0.001
DBP, mmHg	67.0 ± 13.6	65.7 ± 14.6	67.4 ± 12.7	67.1 ± 13.2	67.9 ± 13.9	0.510
MBP, mmHg	82.6 ± 8.3	82.4 ± 8.6	82.9 ± 8.6	83.7 ± 8.3	81.6 ± 7.7	0.113
Heart rate, beats/min	79.0 ± 12.9	84.7 ± 13.9	78.0 ± 12.1	76.8 ± 12.9	76.7 ± 11.0	<0.001
RR, times/min	18.3 ± 3.2	19.2 ± 3.5	18.4 ± 3.6	17.5 ± 3.0	18.1 ± 2.6	<0.001
Temperature, °C	37.0 ± 0.6	37.0 ± 0.7	37.1 ± 0.4	37.0 ± 0.4	37.1 ± 0.6	0.353
SpO2, %	97.5 ± 2.0	97.8 ± 2.3	97.6 ± 1.8	97.4 ± 1.9	97.4 ± 2.0	0.270
Comorbidities, *n* (%)						
Myocardial infarction	58 (8.4)	23 (13.7)	5 (3)	13 (7)	17 (9.7)	0.004
Congestive heart failure	50 (7.2)	15 (8.9)	5 (3)	12 (6.5)	18 (10.3)	0.053
Chronic pulmonary disease	108 (15.6)	26 (15.5)	23 (13.9)	34 (18.4)	25 (14.3)	0.645
Diabetes	88 (12.7)	16 (9.5)	20 (12.1)	19 (10.3)	33 (18.9)	0.036
Hypertension	346 (49.9)	69 (41.1)	77 (46.7)	95 (51.4)	105 (60)	0.004
Paraplegia	100 (14.4)	21 (12.5)	25 (15.2)	27 (14.6)	27 (15.4)	0.868
Sepsis	393 (56.7)	115 (68.5)	82 (49.7)	91 (49.2)	105 (60)	<0.001
Charlson comorbidity index	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)	5.0 (4.0, 7.0)	<0.001
Laboratory results						
WBC,10^9/L	14.5 ± 6.6	16.2 ± 7.7	14.4 ± 6.1	13.6 ± 5.1	14.1 ± 7.1	0.001
Platelets,10^9/L	239.4 ± 90.9	242.0 ± 97.9	243.4 ± 83.4	237.7 ± 92.0	235.1 ± 89.9	0.825
Hemoglobin, g/dL	13.0 ± 1.9	12.9 ± 2.0	13.2 ± 2.0	13.1 ± 1.9	12.7 ± 1.8	0.093
Glucose, mg/dL	142.2 ± 37.9	145.9 ± 46.5	140.0 ± 34.5	138.0 ± 34.1	145.3 ± 35.3	0.133
Sodium, mg/dL	141.8 ± 5.4	142.2 ± 6.3	141.9 ± 4.6	141.4 ± 5.3	141.6 ± 5.2	0.580
Potassium, mg/dL	4.3 ± 0.8	4.4 ± 0.9	4.2 ± 0.7	4.2 ± 0.8	4.2 ± 0.8	0.252
BUN, mg/dL	17.9 ± 10.6	18.4 ± 12.2	16.0 ± 8.4	18.2 ± 11.2	18.8 ± 9.8	0.077
Creatinine, mg/dL	1.0 ± 1.0	1.0 ± 0.8	0.9 ± 0.5	1.1 ± 0.8	1.1 ± 1.4	0.347
Therapy, *n* (%)						
Norepinephrine	180 (26.0)	66 (39.3)	48 (29.1)	31 (16.8)	35 (20)	<0.001
Vasopressin	78 (11.3)	35 (20.8)	20 (12.1)	15 (8.1)	8 (4.6)	<0.001
Dopamine	13 (1.9)	8 (4.8)	2 (1.2)	1 (0.5)	2 (1.1)	0.036
Nicadipine	495 (71.4)	105 (62.5)	115 (69.7)	136 (73.5)	139 (79.4)	0.005
Nimodipine	484 (69.8)	105 (62.5)	120 (72.7)	128 (69.2)	131 (74.9)	0.069
Embolization of aneurysm	202 (29.1)	39 (23.2)	64 (38.8)	54 (29.2)	45 (25.7)	0.010
Clipping of aneurysm	36 (5.2)	10 (6)	9 (5.5)	11 (5.9)	6 (3.4)	0.673
Scoring systems						
GCS	11.0 (7.0, 14.0)	9.0 (4.8, 14.0)	13.0 (6.0, 14.0)	13.0 (8.0, 14.0)	11.0 (7.0, 14.0)	0.006
Outcomes						
28 day mortality	132 (19.0)	43 (25.6)	23 (13.9)	30 (16.2)	36 (20.6)	0.034
ICU mortality	110 (15.9)	38 (22.6)	18 (10.9)	21 (11.4)	33 (18.9)	0.005
Hospital mortality	142 (20.5)	47 (28)	24 (14.5)	33 (17.8)	38 (21.7)	0.016

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; RR, respiratory rate; SpO2, percutaneous oxygen saturation; WBC, white blood cell; GCS, Glasgow coma score; ICU, intensive care unit; SAH, subarachnoid hemorrhage.

TABLE 2 Relationship between baseline pulse pressure and hospital mortality stratified by quartiles and combined quartiles.

Pulse pressure, mmHg	Total	Event (*n*, %)	Crude		Model I		Model II	
			HR (95%CI)	Value of *p*	HR (95%CI)	Value of *p*	HR (95%CI)	Value of *p*
Continuous	693	142 (20.5)	1.00 (0.99, 1.01)	0.503	1.00 (0.99, 1.01)	0.563	0.99 (0.99, 1.00)	0.231
Quartiles								
Q1 (≤56 mmHg)	168	47 (28.0)	1 (Ref)		1 (Ref)		1 (Ref)	
Q2 (57–68 mmHg)	165	24 (14.5)	0.51 (0.31, 0.84)	0.009	0.50 (0.30, 0.82)	0.006	0.55 (0.33, 0.93)	0.026
Q3 (69–82 mmHg)	185	33 (17.8)	0.72 (0.46, 1.13)	0.158	0.62 (0.40, 0.98)	0.041	0.99 (0.62, 1.59)	0.966
Q4 (≥83 mmHg)	175	38 (21.7)	0.89 (0.58, 1.37)	0.604	0.67 (0.43,1.05)	0.078	0.99 (0.62, 1.57)	0.954
Categories								
Q1 (≤56 mmHg)	168	47 (28.0)	1.95 (1.19, 3.22)	0.009	2.02 (1.22, 3.34)	0.006	1.85 (1.11, 3.10)	0.019
Q2 (57–68 mmHg)	165	24 (14.5)	1(Ref)		1(Ref)		1(Ref)	
Q3–4 (≥69 mmHg)	360	71(39.5)	1.57 (0.98, 2.52)	0.059	1.31 (0.81, 2.11)	0.271	1.78 (1.08, 2.93)	0.024

HR, hazard ratio; Q, quartile. Crude: no covariates were adjusted; Model I: adjusted for age, sex, and ethnicity. Model II: adjusted for age, sex, ethnicity, RR, WBC, platelet, GCS score, Charlson Comorbidity Index, congestive heart failure, myocardial infarction, hypertension, sepsis, vasoactive drugs, nicardipine, nimodipine, embolization of aneurysms. CI, confidence interval; HR, hazards ratio; Ref, reference.

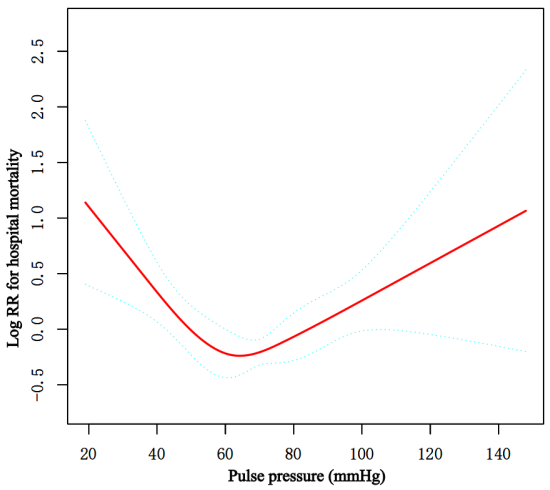

FIGURE 2
Associations between the baseline PP level and in-hospital mortality in critically ill patients with non-traumatic SAH. A threshold, nonlinear association between the baseline PP level and hospital mortality was found in restricted cubic spline (RCS). Solid rad line represents the smooth curve fit between variables. Green bands represent the 95% of confidence interval from the fit. Adjusted for age, sex, ethnicity, RR, WBC, platelet, GCS score, Charlson Comorbidity Index, congestive heart failure, myocardial infarction, hypertension, sepsis, vasoactive drugs, nicardipine, nimodipine, embolization of aneurysms. PP, pulse pressure; SAH, subarachnoid hemorrhage.

nicardipine, nimodipine, and aneurysm embolization in the Model II. In any of the three models (all $p > 0.05$), there was no significant relationship between the baseline PP level and hospital mortality when it was used as a continuous variable. Overall, the association between baseline PP Level and hospital mortality followed a nonlinear curve using a smooth curve function in Figure 2 ($p = 0.041$). Accordingly, when baseline PP Level was assessed in quartiles and compared with Q1 (<56 mmHg), the risk of hospital mortality was lower for Q2 (57 to ≤68 mmHg: adjusted HR, 0.99; 95% CI, 0.62–0.93; $p = 0.026$), Q3 (69 to ≤82 mmHg: adjusted HR, 0.99; 95% CI, 0.62–1.59; $p = 0.966$), and Q4 (≥83 mmHg: adjusted HR, 0.99; 95% CI, 0.62–1.57; $p = 0.954$) (Table 2). The lowest risk of hospital mortality was found in those in Q2. When quartiles were combined in a further exploratory study, a significantly higher risk of hospital mortality was found among patients in Q1 (<56 mmHg: adjusted HR, 1.85; 95% CI, 1.11–3.10; $p = 0.019$) and in Q3–4 (≥69 mmHg: adjusted HR, 1.78; 95% CI, 1.08–2.93; $p = 0.024$) compared to those in Q2 (57 to ≤68 mmHg) (Table 2).

Moreover, the K-M curves contrasting the three groups were displayed in Figure 3. The figure indicated that the survival rate of group Q2 was higher than groups Q1and Q3 ($p = 0.041$).

The results of the two-piecewise linear regression model

Piecewise multivariate Cox regression with two different slopes was used to confirm the relationship between PP at baseline and in-hospital mortality. In the threshold analysis, for every 5 mmHg increase in PP level, there was an 18.2% decrease in hospital mortality (adjusted HR, 0.818; 95% CI, 0.738–0.907; $p = 0.0001$) in those with PP level 60 mmHg, and a 7.7% increase in hospital mortality (adjusted HR, 1.077; 95% CI, 1.018–1.139; $p = 0.0096$) in those with PP level 60 mmHg or higher. The linear regression model and a two-piecewise linear regression model were compared, and the p value of the log-likelihood ratio test was <0.001 (Table 3 and Figure 2).

Subgroup analysis

We performed further stratified and interaction analysis to assess the association between baseline PP level (Q1 vs. Q2 vs. Q3–4) and the risk of hospital mortality in various subgroups (Table 4): sex (male vs. female), myocardial infarction (no vs. yes), congestive heart failure (no vs. yes), hypertension (no vs. yes),

diabetes (no vs. yes), endovascular therapy of aneurysm (no vs. yes), GCS (<8 and ≥8) results. The non-linear association was consistent across all subgroups, except for diabetes. The stratified analysis demonstrated association between baseline PP level and the risk of hospital mortality subjects without diabetes [(adjusted HR, 1.912; 95% CI, 1.090–3.353) vs. (1) vs. (adjusted HR, 1.601; 95% CI, 0.920–2.785)], with diabetes [(adjusted HR, 0.543; 95% CI, 0.080 3.705) vs. (1) vs. (adjusted HR, 2.146 95% CI, 0.499, 9.228)]. Overall, the interaction analysis revealed no interactive role in the association between baseline PP level and hospital mortality (P for interaction >0.05).

In the Supplementary analysis, we also examined the relationship between baseline PP levels, the 28 day mortality, and ICU mortality. Both 28 day and ICU mortality had a non-liner relationship with baseline PP levels (Supplemental Figure S1; Figure 2).

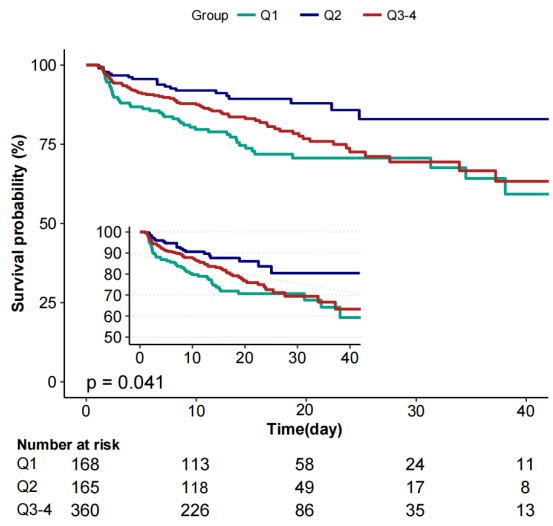

FIGURE 3
Kaplan–Meier survival curves for critically ill patients with non-traumatic SAH based on baseline PP level. *X*-axis: survival time (days). *Y*-axis: survival probability. PP, pulse pressure; SAH, subarachnoid hemorrhage.

Discussion

In this retrospective cohort study of ICU patients with non-traumatic SAH, we found a nonlinear association between the admission PP level and hospital mortality after adjusting for baseline covariates, with an inflection point at approximately 60 mmHg and minimal risk at 57 to 68 mmHg of the admission PP level.

The relationship between PP level in the acute phase of stroke and outcomes has been investigated in some studies. Grabska et al. and Su et al. examined PP levels and 30 day mortality, and they discovered that elevated PP levels were associated with an increased risk of 30 day mortality (11, 12). Domanski et al. reported that for every 10 mmHg increase in pulse pressure, there was an 11% increase in the risk of stroke and a 16% increase in the risk of all-cause mortality in elderly patients with systolic hypertension (5). A post-hoc analysis of 1,479 patients from the TAIST (Tinzaparin in Acute Ischaemic Stroke Trial) found that elevated PP upon admission among patients within 48 h of ischemic stroke was independently linked to mortality (odds ratio, 1.02; 95% CI, 1.01–1.03) (7). Vemmos et al. discovered that every 10 mm Hg increase in 24 h PP levels resulted in higher mortality (HR, 1.39; 95% CI, 1.04–1.86) for 1 year during the acute stroke period (9). According to our investigation, when the admission PP level was ≥105 mmHg, a 5 mm Hg increase in PP upon admission corresponded to a 39% increased risk of hospital mortality (HR, 1.39; 95% CI, 1.05–1.83) after non-traumatic SAH. In a study of 672 patients with non-traumatic cerebral hemorrhage (ICH), Jason et al. discovered that the higher PP levels (first 12 h mean PP) after admission were linked to increased in-hospital mortality (odds ratio, 3.0; 95% CI, 1.7–5.3) (8). However, there are few studies on the association between PP level and mortality in SAH patients. A previous study including 156 patients with SAH demonstrated no statistically significant association between admission PP and hospital mortality (13). Contrary to these results, our study demonstrated that a higher or lower PP upon admission was associated with an increased risk of hospital mortality. Similar results were seen among non-traumatic SAH patients with HF, hypertension, and embolization of an aneurysm, even if vasopressor requirements were considered. These results highlight the role of the pulsatile element of BP and the importance of ensuring constant perfusion and cardiac function on post-SAH outcomes. Also, it suggests that the importance of admission PP level extends beyond the non-surgical population alone. In support of our findings, a Taiwan

TABLE 3 Threshold effect analysis of pulse pressure and hospital mortality.

Models	Per-1mmHg increase		Per-5mmHg increase	
	HR (95%CI)	*p* value	HR (95%CI)	*p* value
Model I				
One line effect	0.999 (0.990, 1.007)	0.7778	0.994 (0.952, 1.037)	0.7778
Model II				
Turning point (K, mmHg)	60		12	
pulse pressure < *k*	0.964 (0.946, 0.983)	0.0001	0.818 (0.738, 0.907)	0.0001
pulse pressure ≥ *k*	1.016 (1.004, 1.028)	0.0096	1.077 (1.018, 1.139)	0.0096
P value for LRT test*		<0.001		<0.001

Data were presented as HR (95% CI) *p* values; Model I, linear analysis; and Model II, non-linear analysis. Adjusted for age, sex, ethnicity, RR, WBC, platelet, GCS score, Charlson Comorbidity Index, congestive heart failure, myocardial infarction, hypertension, sepsis, vasoactive drugs, nicardipine, nimodipine, embolization of aneurysms. CI, confidence interval; HR, hazards ratio; LRT, logarithm likelihood ratio test. *$P < 0.05$ indicates that Model II is significantly different from Model I.

TABLE 4 The subgroup analysis for baseline pulse pressure on hospital mortality.

Subgroup	Total	Event (*n*, %)	Categories of the baseline pulse pressure, adjusted HR (95% CI)			P for interaction
			Low (≤56mmHg)	Reference (57–68mmHg)	High (≥69mmHg)	
Sex						0.876
Male	389	73 (18.8)	1.923 (0.927, 3.99)	1	1.814 (0.899, 3.661)	
Female	304	69 (22.7)	1.629 (0.766, 3.467)	1	1.613 (0.769, 3.384)	
Myocardial infarction						0.907
No	635	121 (19.1)	1.836 (1.063, 3.168)	1	1.765 (1.042, 2.991)	
Yes	58	21 (36.2)	1.382 (0.148, 12.94)	1	1.144 (0.116, 11.28)	
Congestive heart failure						0.111
No	643	121 (18.8)	1.747 (1.024, 2.980)	1	1.459 (0.866, 2.461)	
Yes	50	21 (42.0)	3.767 (0.228, 62.26)	1	11.23 (0.826, 152.62)	
Hypertension						0.601
No	347	77 (22.2)	1.360(0.658, 2.812)	1	1.811 (0.890, 3.686)	
Yes	346	65 (18.8)	2.101 (0.978, 4.514)	1	1.142 (0.557, 2.338)	
Diabetes						0.154
No	605	117 (19.3)	1.912 (1.090, 3.353)	1	1.601 (0.920, 2.785)	
Yes	88	25 (28.4)	0.543 (0.080, 3.705)	1	2.146 (0.499, 9.228)	
Embolization of aneurysm						0.743
No	491	116 (23.6)	1.975 (1.093, 3.570)	1	1.940(1.087, 3.463)	
Yes	202	26 (12.9)	1.454 (0.421, 5.024)	1	1.333 (0.452, 3.929)	
GCS score						0.503
<8	219	81 (37)	1.084 (0.555, 2.117)	1	1.272 (0.668, 2.422)	
≥8	474	61 (12.9)	1.519 (0.575, 4.011)	1	1.952 (0.826, 4.614)	

The model was adjusted, if not stratified, for age, sex, ethnicity, RR, WBC, platelet, GCS score, Charlson Comorbidity Index, congestive heart failure, myocardial infarction, hypertension, sepsis, vasoactive drugs, nicardipine, nimodipine, embolization of aneurysms.

prospective cohort study of 33,530 individuals aged >18 years found a U-shaped association between PP at admission and a 3 month unfavorable outcome in acute ischemic stroke (10). We also observed a threshold effect. The non-traumatic SAH patients with PP upon admission range of 57 to 68 mmHg were at the lowest risk of mortality. Our study suggests that maintaining PP goals lower than about 60 mmHg may not be adequate to preserve organ perfusion. However, compared to previous studies, first, our study assessing PP based on the non-traumatic SAH population was larger. Second, the disease severity in the study population may have been different as it was from the ICU. Third, the adjustment variables were also different, and we adjusted for several well-known outcome parameters, disease severity, ICU treatment, and comorbidities of common serious illnesses. Furthermore, this may have implications for SAH BP management and warrants further investigation.

The potential underlying mechanisms behind the close correlation between the admission PP level and hospital mortality in ICU patients with non-traumatic SAH are still unknown. Potential mechanisms are presented below. First, the PP level depends on the vascular elasticity of the systolic ejection dilation catheter arteries and the large arteries (27–31). Thus, the level of PP indirectly reflects the degree of arterial stiffness. Furthermore, increased PP is common in high-risk patients with large artery stiffness, aortic regurgitation, and increased systolic hypertension (6, 32). Second, elevated PP value might lead to greater cyclic strain that induces inflammatory endothelial cell responses, increasing the risk of inflammatory-related diseases such as atherosclerotic cardiovascular disease (33). Thirdly, recent studies have found that a high PP would produce non-steady shear stress forces. This non-steady shear might well result in oscillatory (i.e., reversing or 'back-and-forth') shear stress forces, particularly at arterial branch points during which blood flow is still non-steady due to branch point geometry (34). Fourth, a low PP may be indicative of lower CBF due to impaired cerebral autoregulation or reduced cerebral perfusion, which could increase the risk of cerebral vasospasm (35). Interestingly, we found an inconsistent relationship between PP and in-hospital mortality rates in SAH patients with and without diabetes. We conducted further investigation into this phenomenon. The increased risk of in-hospital mortality in diabetic patients with higher PP may be attributed to several factors. Firstly, diabetic patients often have multiple cardiovascular diseases and complications, such as hypertension, coronary heart disease, and heart failure, which may affect the relationship between PP and mortality. Secondly, diabetic patients often have pathological and physiological changes, such as endothelial dysfunction and vascular damage, which may lead to arterial stiffness and increased vascular resistance, thereby increasing the risk of cardiovascular events and death (29, 36). Additionally, metabolic abnormalities such as hyperglycemia and insulin resistance in diabetic patients may affect vascular contraction and relaxation,

thereby influencing the magnitude of PP and its impact on cardiovascular events (37, 38). In conclusion, there are specific physiological and metabolic changes in the relationship between PP and in-hospital mortality in diabetic patients, which require further research to explore their specific mechanisms. Overall, the factors affecting PP mentioned above may increase the risk of adverse outcomes in SAH patients, and the exact mechanisms need to be investigated further.

Our study has several limitations. First, we utilized data from the ICU Medical Center in the United States, and because this was a single-center study, the results may not be completely representative of the general non-traumatic SAH patient population. Second, this was a retrospective cohort study with limitations such as the possibility of unmeasured confounders and missing data influencing the results. Furthermore, admission diagnoses are premised on ICD-9 and ICD-10 codes, which may undercount the number of patients suffering from non-traumatic SAH and related complications. As a result, we conducted a sensitivity analysis that included some interventions and common comorbidities. Fortunately, the sensitivity analysis result remained consistent. Third, because PP data were limited to baseline values at ICU admission, this study could only confirm the correlation between admission PP levels and hospital mortality without establishing a causal relationship. Four, we analyzed the first PP record collected during ICU admission, and therefore, the results are limited to a confined period during which PP was measured. In addition, the blood pressure values obtained from the MIMIC database may have been collected using equipment from different manufacturers. Therefore, there is no way to accurately standardize blood pressure measurement. However, each medical unit regularly calibrated monitors to prevent errors in medical practice.

Conclusion

For patients with non-traumatic SAH, the association between baseline PP and risk of hospital mortality was non-linear, with an inflection point at 60 mmHg and a minimal risk at 57 to 68 mmHg (Q2) of baseline PP level. If further confirmed, our findings provides evidence for the early identified high risk of hospital mortality in non-traumatic subarachnoid hemorrhage population.

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

The studies involving human participants were examined and approved by Beth Israel Deaconess Medical Center. To protect patient privacy, all data were de-identified; therefore, the Ethical Committee of the Beth Israel Deaconess Medical Center waived the requirement for informed consent. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

HZ and XW conceived the study idea. JL and HZ analyzed the data, reviewed the literature, and wrote the first draft. LJ and SW critically reviewed and edited the manuscript and approved the final version. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1176546/full#supplementary-material

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Nimodipine systemic exposure and outcomes following aneurysmal subarachnoid hemorrhage: a pilot prospective observational study (ASH-1 study)

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Background: Nimodipine improves outcomes following aneurysmal subarachnoid hemorrhage (aSAH). Guidelines recommend that all patients should receive a fixed-dose nimodipine for 21 days. However, studies reported variability of nimodipine concentrations in aSAH. It is not clear if reduced systemic exposure contributes to worsening outcomes. The aim of this study was to compare nimodipine systemic exposure in those who experienced poor outcomes to those who experienced favorable outcomes.

Methods: This was a pilot prospective observational study in 30 adult patients admitted to the University of Alberta Hospital with aSAH. Data were collected from the electronic health records following enrollment. Blood samples were collected around one nimodipine 60 mg dose at a steady state, and nimodipine [total, (+)-R and (–)-S enantiomers] plasma concentrations were determined. The poor outcome was defined as a modified Rankin Scale (mRS) score at 90 days of 3-6, while the favorable outcome was an mRS score of 0-2. The correlation between nimodipine concentrations and percent changes in mean arterial pressure (MAP) before and after nimodipine administration was also determined. Furthermore, covariates potentially associated with nimodipine exposure were explored.

Results: In total, 20 (69%) participants had favorable outcomes and 9 (31%) had poor outcomes. Following the exclusion of those with delayed presentation (>96 h from aSAH onset), among those presented with the World Federation of Neurological Surgeons (WFNS) grade 3–5, nimodipine median (interquartile range) area under the concentration time curve ($AUC_{0\text{-}3h}$) in those with favorable outcomes were 4-fold higher than in those with poor outcomes [136 (52–192) vs. 33 (23–39) ng.h/mL, respectively, value of $p = 0.2$]. On the other hand, among those presented with WFNS grade 1–2, nimodipine $AUC_{0\text{-}3h}$ in those with favorable outcomes were significantly lower than in those with poor outcomes [30 (28–36) vs. 172 (117–308) ng.h/mL, respectively, value of $p = 0.03$)]. (+)-R-nimodipine $AUC_{0\text{-}3h}$ in those

who did not develop vasospasm were 4-fold significantly higher than those who had vasospasm (value of $p = 0.047$). (−)-S-nimodipine was significantly correlated with percentage MAP reduction. Similar results were obtained when the whole cohort was analyzed.

Conclusion: The study was the first to investigate the potential association between nimodipine exposure following oral dosing and outcomes. In addition, it suggests differential effects of nimodipine enantiomers, shedding light on the potential utility of nimodipine enantiomers. Larger studies are needed.

KEYWORDS

nimodipine, aneurysmal subarachnoid hemorrhage, pharmacokinetics, vasospasm, delayed cerebral ischemia, modified Rankin scale

1 Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a critical neurological condition caused by the rupture of a cerebral blood vessel aneurysm, leading to bleeding into the subarachnoid space. Although aSAH accounts for 5% of all strokes, given the relatively young age at onset, it has a significant burden on patients' productive life years. The average mortality rate for aSAH has been reported to range from 30 to 50%, leaving a significant proportion of survivors with disabilities (1–3). Neurological and medical complications following aSAH contribute significantly to the overall prognosis. The main complications secondary to aSAH significantly contributing to disability and unfavorable patient outcomes are delayed cerebral ischemia (DCI) and vasospasm. A substantial amount of research has been done with the aim of understanding the mechanisms of these complications and exploring potential therapeutic modalities for the sake of improving patient outcomes (4, 5). Several agents have been investigated to target vasospasm and DCI; however, nimodipine has been the only drug therapy that has been shown to significantly reduce the incidence of DCI secondary to aSAH and subsequently improves neurological outcomes post aSAH [relative risk 0.67 (95% CI 0.55–0.81)] (6–11). Therefore, nimodipine, a dihydropyridine calcium channel blocker with preferential effects on cerebral blood vessels, is currently considered a standard of care in aSAH management (Class I; Level of Evidence A) (2, 3).

American Heart Association (AHA) and Neurocritical Care Society guidelines recommend that all patients presenting with aSAH should receive a fixed dose of oral nimodipine 60 mg every 4 h for 21 days from aSAH onset (2, 3). Pharmacokinetic studies have reported extensive variability of nimodipine concentrations in various populations and in the setting of aSAH, with some patients having undetectable nimodipine plasma levels (12–17). The observed variability in nimodipine exposure may have been attributed to practice variations in nimodipine administration, systemic inflammation, disease severity, administration of concomitant interacting drugs, and cytochrome P450 polymorphism (17–22). While previous randomized controlled trials have found that nimodipine reduces the incidence of poor neurologic outcomes (defined by death, persistent vegetative state, and severe disability) by 40–86%, a significant proportion of patients in the nimodipine arm experienced poor outcomes (10, 23, 24). Therefore, it is not clear if all patients are getting the full benefit of nimodipine using a fixed-dose regimen. However, no prior studies have investigated whether an association exists between plasma nimodipine concentrations following oral dosing and clinical outcomes.

The aim of this pilot study was, hence, bi-faceted. The primary aim was to compare nimodipine systemic exposure in aSAH patients who experienced poor outcomes with those who experienced favorable outcomes at 90 days following aSAH. Poor outcomes were defined as modified Rankin Scale (mRS) score of 3–6, and favorable outcomes were defined as an mRS score of 0–2. Nimodipine systemic exposure was quantified using the area under the concentration-time curve at a steady state from 0 to 3 h ($AUC_{0\text{-}3h}$) following a 60 mg oral dose. Furthermore, nimodipine maximum concentrations (C_{max}) were compared as surrogate measures of $AUC_{0\text{-}3h}$. The secondary aim was to identify covariates that are potentially associated with the observed nimodipine systemic exposure. This is through exploring trends in nimodipine concentrations categorized by different covariates. Since nimodipine is a chiral compound, we aimed to investigate the above comparisons for total nimodipine as well as both (+)-S and (−)-R enantiomers. To the best of our knowledge, this is the first study to report such comparisons.

2 Materials and methods

2.1 Study design

This was a pilot single-center prospective observational study. The study was approved by the Health Research Ethics Board of the University of Alberta, and informed consent was obtained from participants or from their substitute decision-makers (SDM). Patient recruitment occurred from June 2019 to February 2022.

2.2 Study population

Adult patients admitted to the Neuroscience Intensive Care Unit (ICU) at the University of Alberta Hospital and diagnosed with aSAH were included in the study. The inclusion criteria included aSAH patients aged 18–85 years who were receiving nimodipine 60 mg every 4 h either orally (PO) or through a feeding tube (FT) and presence of

an intravascular catheter at the time of sampling to facilitate frequent blood withdrawals. The exclusion criteria were anticipated hospital length of stay of less than 48 h and non-aneurysmal SAH. Since our aims were exploratory and there was no similar work to this pilot study, we planned to enroll a convenient sample of 30 participants.

2.3 Data collection

Data were collected prospectively from the electronic health records following participants' enrollment. Study data were managed using the REDCap (25, 26) electronic data capture tool hosted at the University of Alberta. The collected data included participants' demographics [age, sex, height, weight, and body mass index (BMI)], pre-admission disability, history of hypertension, diabetes, chronic kidney disease, migraine, and liver disease (liver cirrhosis or Child Pugh class B or C). In addition, admission Glasgow coma score (GCS), Fisher scale, and World Federation of Neurological Surgeons (WFNS) grade were collected. Aneurysm location and treatment (e.g., endovascular coiling and surgical clipping) were also collected. The nimodipine administration record was also collected and included dose, frequency, duration, and route of administration (PO vs. FT). The administration and duration of liver microsomal enzyme (LME) inducing and inhibiting medications were recorded for the first 21 days of hospital stay or until discharge, whichever came first.

2.3.1 Study outcomes

The primary clinical outcome collected was the mRS score at 90 days following aSAH. Participants' mRS scores at 90 days were collected by contacting the participant or their SDM. The mRS is a measure of disability ranging from 0 (no symptoms at all) to 6 (dead), and it is the recommended functional outcome scale in clinical studies involving aSAH patients (27–29). A 90-day time period is the most common time frame for acute stroke trials (including aSAH) (30). Poor functional outcomes were defined as an mRS score of 3–6, and favorable outcomes were defined as an mRS score of 0–2.

Secondary clinical outcomes included delayed cerebral ischemia (DCI), vasospasm, and hospital mortality. DCI was defined according to Vergouwen et al. as "the occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect) or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 h, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies" (31). Vasospasm was defined as the presence of angiographic evidence of cerebral arterial narrowing (moderate to severe) as determined by the neuroradiologist utilizing digital subtraction angiography (DSA). Additional outcomes recorded included the length of stay in the hospital and ICU as well as the discharge disposition.

2.4 Study procedures

2.4.1 Sample collection

Blood samples were collected at approximately one nimodipine 60 mg dose at a steady state. Since the reported half-life of nimodipine ranges from 1 to 2 h, and it generally takes 3 to 5 half-lives for a drug to achieve a steady state, we assumed that a steady state was reached after a minimum of 24 h of consistent dosing with a regimen of 60 mg every 4 h (17, 32). Blood samples (5 mL each) were collected at times 0 (just before the administration of nimodipine dose), 0.5, 1, 2, and 3 h following the administration of nimodipine dose. Samples were collected from an already established intravascular catheter (as part of the standard of care in our institution) by the bedside nurse in light-protected blood collection tubes (K2EDTA Vacutainer® lavender top, BD, San Jose, CA, USA). Samples were then sent to Alberta Precision Laboratories (APL) for processing and separation of plasma. Plasma samples were aliquoted into light-protected tubes and subsequently frozen at −70°C. Frozen samples were then transported to the principal investigator (S.H.M.) laboratory and stored at −80°C until analysis. To determine if nimodipine plasma concentrations were correlated with the intensity of blood pressure reduction, participants' mean arterial pressure (MAP) values measured around the sampling nimodipine dose (as part of the standard of care) were also collected.

2.4.2 Nimodipine plasma concentration determination

Nimodipine enantiomers [(−)-S and (+)-R] plasma concentrations were measured using an LC–MS/MS method validated at the principal investigator (S.H.M.) lab (33). Briefly, 300 µL of plasma samples or standard were added to 50 µL of the internal standard nifedipine (50 ng/mL), followed by alkalinization with 200 µL of 1 M sodium hydroxide. Aliquots of 4 mL of diethylether/hexane (1:1) were added, and the vortex was mixed for 5 min. The samples were then centrifuged at 2000 rpm for 10 min and frozen in a −80 freezer for 20 min to separate the organic layer from the aqueous layer. Aliquots of the organic layer were transferred to clean tubes and evaporated to dryness under vacuum and no heating. Then, the residues were reconstituted in 125 µL of the mobile phase, and 40 µL were injected into the LC–MS/MS at a flow rate of 1 mL/min. The mobile phase consisted of methanol:water (75:25). The analysis was conducted using Shimadzu LC–MS/MS-8050 (Shimadzu Corporation, Kyoto, Japan) with a CBM-20A system controller, DGU-20A 5R degasser unit, SIL-30-AC autosampler, LC-30 AD binary pump, CTO-20 AC column oven, and LCMS-8050 triple quadrupole mass spectrometry detector. The chromatographic separation was carried out using an (S,S)-Whelk O1 (5 µm, 250 × 4.6 mm) chiral stationary phase column (Regis Technologies Inc., Morton Grove, IL, USA) with a KrudKatcher® Ultra guard column (Phenomenex, Torrance, CA, USA). LabSolutions® software version 5.91 (Shimadzu Kyoto, Japan) was utilized for data acquisition and chromatographic integration. The samples were run in singlets. During our assay development, running standard nimodipine samples consistently yielded equivalent peak ratios for the two enantiomers, indicating an equal quantity of each enantiomer in racemic nimodipine. The analytical method had intra- and inter-day coefficient of variation and percentage error within ±14%. Total nimodipine plasma concentrations were calculated by adding the values of (−)-S and (+)-R enantiomers concentrations at each time point. To eliminate bias, the analysts were blinded to the patients' baseline characteristics.

2.4.3 Plasma inflammatory markers determination

To determine whether markers of systemic inflammation are potentially associated with nimodipine exposure and patient

outcomes, aliquots of the collected plasma samples were utilized to determine plasma cytokines by using commercially available ELISA kits (Invitrogen Co., Waltham, Massachusetts, United States). Cytokines included interleukin (IL-6), IL-1β, and tumor necrosis factor alpha (TNF-α), three markers potentially implicated with aSAH pathophysiology (34–36). The assays were conducted as per the manufacturer's instructions. UV absorbance was measured using the Synergy H1 Hybrid Multi-Mode Plate Reader (BioTek Instruments, Inc., CA, United States).

2.5 Data analysis

Participants' baseline characteristics, hospital course, outcomes, inflammatory markers, and nimodipine dosing were summarized. Continuous variables were presented as mean ± standard deviation (SD) if data were normally distributed and compared using the Student t-test. Alternatively, they were presented as median and interquartile range (IQR) if data were not normally distributed and compared using the Wilcoxon rank sum test. The Shapiro–Wilk test was utilized to assess the normality of continuous data. Categorical variables were presented as frequency and percentage n (%) and were compared using the χ^2 or Fisher exact test, as appropriate. Nimodipine systemic exposure was quantified using the area under the concentration-time curve at a steady state from 0 to 3 h ($AUC_{0\text{-}3h}$) following a 60 mg oral dose. Individual $AUC_{0\text{-}3h}$ were calculated from nimodipine concentration-time data using the linear trapezoidal method utilizing PKanalix® software version 2021R1 (Lixoft, Antony, France). Furthermore, nimodipine maximum (C_{max}) and minimum (C_{min}) concentrations were determined from nimodipine concentration-time data. The correlations of MAP percentage drop, calculated as the difference in pre-dose MAP and the lowest MAP value within 2 h of nimodipine administration divided by pre-dose MAP multiplied by 100, with total, (−)-S and (+)-R nimodipine C_{max} were determined using Pearson's correlation coefficient. Median $AUC_{0\text{-}3h}$ and C_{max} were compared between those with poor outcomes (mRS of 3–6) and those with favorable outcomes (mRS of 0–2) using the Wilcoxon rank sum test. To check if nimodipine enantiomers have differential effects, the above comparisons were also conducted for both (−)-S and (+)-R enantiomers. The contribution of various covariates on nimodipine exposure was determined using categorization. Explored covariates were age, BMI, presence of interacting drugs, liver disease, WFNS grade, inflammatory mediators, and nimodipine route of administration. Missing data, if any, were handled by complete case analysis. A value of p of <0.05 was considered statistically significant. Data analysis was conducted using STATA software version 15 (STATA Corporation, College Station, TX, USA).

3 Results

A total of 31 participants were recruited. One participant had their intravascular catheter removed and was sent to the ward just after enrollment. Therefore, 30 participants were included in the current study. Table 1 depicts the baseline characteristics of the included participants. Females comprised 60% of the study participants, and the mean age of the cohort was 57 ± 12.1 years. All participants were without baseline disability (i.e., preadmission mRS of 0). Forty percent of the participants presented with poor grade aSAH (WFNS of 3-5). Two-thirds of the ruptured aneurysms were secured by endovascular coiling (63.3%), while the remaining 36.7% were secured by surgical clipping. All participants received nimodipine treatment within the first 24 h of hospital admission with a median (IQR) duration of 14.5 (12–20) days. A summary of nimodipine dosing in the current study is shown in Table 2.

3.1 Study outcomes

All participants had their 90-day mRS recorded except one patient was lost to follow-up. Twenty participants (69%) had favorable outcomes (mRS of 0–2) and 9 (31%) had poor outcomes (mRS of 3-6). Comparison of the baseline characteristics and nimodipine dosing of those who had poor outcomes to those who had favorable outcomes are depicted in Tables 1, 2, respectively. Compared to the favorable outcome group, participants' who had poor outcomes were older (64.3 ± 8.2 vs. 55.5 ± 9.9 years, value of p 0.027), had higher prevalence of hypertension, and had lower admission GCS. In terms of nimodipine treatment course completion, the ratio of the number of days of nimodipine treatment divided by the hospital length of stay or 21 days, whichever is shorter was multiplied by 100, and both groups had similar median treatment course percentages (100%) (Table 2).

All participants but one had DSA conducted, where 15 participants (50%) had angiographic evidence of vasospasm and 8 (26.7%) developed DCI. One patient did not undergo angiography, but transcranial Doppler (TCD) showed severe vasospasm and CT had multiple infarcts and therefore was coded to have VSP and DCI. A total of 20 (66.7%) participants had mechanical ventilation with a median (IQR) duration of 1 (0–3) day for the whole cohort. A total of 18 (60%) participants had hydrocephalus and had an external ventricular drain (EVD) for a median (IQR) duration of 10.5 (0–14) days for the whole cohort. Median (IQR) ICU and hospital stays were 13.5 (8–18) and 18 (12–24) days, respectively.

3.2 Nimodipine plasma concentrations

All participants had five blood samples collected around a 60 mg dose at the steady state, with the exception of one participant who only had two samples collected and was consequently excluded from the pharmacokinetic calculations. The sampling days ranged from 2 to 11 days following nimodipine initiation, with a median (IQR) of 4 (3–6) days. Six (20%) participants were receiving nimodipine via the feeding tube and others orally. A large variability in total, (−)-S and (+)-R nimodipine enantiomer concentrations was observed (Table 3; Figure 1). (−)-S-nimodipine plasma concentrations were approximately 3-fold lower than the (+)-R enantiomer. Both C_{max} and C_{min} for total nimodipine were strongly correlated with $AUC_{0\text{-}3h}$ ($r = 0.92$, value of $p < 0.001$ for C_{max} vs. $AUC_{0\text{-}3h}$; $r = 0.97$, value of $p < 0.001$ for C_{min} vs. $AUC_{0\text{-}3h}$), suggesting that C_{max} and C_{min} could be utilized as surrogate measured of $AUC_{0\text{-}3h}$. Similar associations were present for both (−)-S and (+)-R enantiomers.

TABLE 1 Baseline characteristics of the enrolled participants.

Characteristic	All cohort ($n = 30$)	mRS 90d 0-2 ($n = 20$)	mRS 90d 3-6 ($n = 9$)	Value of p
Age (years)	57 ± 12.1	55.5 ± 9.9	64.3 ± 8.2	**0.027**
Females	18 (60)	12 (60)	5 (55.6)	1.0
Height (cm)	172.4 ± 11.8	172.5 ± 8.9	172.5 ± 17.6	0.998
Weight (kg)	81.2 ± 22.9	80.6 ± 21.2	85.3 ± 27	0.619
BMI	27.2 ± 6.7	27 ± 6.6	28.3 ± 6.9	0.645
Hypertension	11 (36.67)	5 (25)	6 (66.67)	**0.048**
Delayed presentation	5 (16.67)	5 (25)	0 (0)	0.153
Aneurysm location				**0.034**
MCA	6 (20)	6 (30)	0 (0)	
ACOM	8 (26.67)	3 (15)	4 (44.44)	
PCOM	6 (20)	5 (25)	1 (11.11)	
BASILAR	2 (6.67)	0 (0)	2 (22.22)	
OTHER LOCATION	8 (26.67)	6 (30)	2 (22.22)	
Aneurysm treatment				0.237
Coiling	19 (63.33)	14 (70)	4 (44.44)	
Clipping	11 (36.67)	6 (30)	5 (55.56)	
Fisher Scale				0.082
2	8 (26.67)	7 (35)	0 (0)	
3	4 (13.33)	3 (15)	1 (11.11)	
4	18 (60)	10 (50)	8 (88.9)	
Admission GCS	14 (14–15)	14.5(14–15)	14 (12–14)	**0.015**
WFNS grade				0.130
1	11 (36.67)	10 (50)	1 (11.11)	
2	7 (23.33)	4 (20)	2 (22.22)	
3	8 (26.67)	5 (25)	3 (33.33)	
4	3 (10)	1 (5)	2 (22.22)	
5	1 (3.33)	0 (0)	1 (11.11)	
Poor WFNS (grades 3–5)	12 (40%)	6 (30)	6 (66.67)	0.106

Categorical variables are presented as n (%), while continuous variables are presented as mean ± standard deviation. Admission GCS is presented as median (interquartile range). Those who had favorable (0–2) modified Rankin scale at 90 days (mRS 90d) and poor (3-6) mRS 90d were compared. None of the patients had chronic kidney disease, acute kidney injury, or liver disease. One patient had diabetes type II and was in the poor mRS group. All patients had a baseline mRS of 0. Delayed presentation was defined as presentation to the hospital > 96 h from symptom onset. ACOM, anterior communicating artery; GCS, Glasgow Coma Score; MCA, middle cerebral artery; PCOM, posterior communicating artery; WFNS, World Federation of Neurological Surgeons. WFNS grades of 3 to 5, we considered poor (high) grade; otherwise, they are considered low grade. One participant was lost to follow-up and thus was excluded from mRS comparisons. Bold values, statistically significant.

TABLE 2 Nimodipine dosing history in the enrolled participants.

Characteristic	All cohort ($n = 30$)	mRS 90d 0-2 ($n = 20$)	mRS 90d 3-6 ($n = 9$)	Value of p
Number of days of nimodipine	14.5 (12–20)	13.5 (11.5–19.5)	20 (14–21)	0.306
Days on nimodipine 60 mg PO	12.5 (9–18)	13.5 (10.5–18.5)	5 (0–17)	0.09
Days on nimodipine 30 mg PO	0 (0–0)	0 (0–0)	0 (0–0)	0.966
Days on nimodipine 60 mg FT	0 (0–3)	0 (0–0)	5 (0–13)	**0.004**
Days on nimodipine 30 mg FT	0 (0–0)	0 (0–0)	0 (0–1)	0.26
Nimodipine exposure (%)	100 (95–100)	100 (100–100)	100 (95–100)	0.451

Data are presented as median (interquartile range). Those who had favorable (0-2) modified Rankin scale at 90 days (mRS 90d) and poor (3-6) mRS 90d were compared. Nimodipine exposure was calculated as a percentage: the ratio of number of days of nimodipine divided by the hospital length of stay or 21 days, whichever shorter multiplied by 100. FT, administered via feeding tube; PO, administered orally. One participant was lost to follow up and thus was excluded from mRS comparisons. Bold values, statistically significant.

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TABLE 3 Nimodipine pharmacokinetic parameters.

Parameter*	(–)-S nimodipine			(+)-R nimodipine			Total nimodipine		
	Median (IQR)	Min	Max	Median (IQR)	Min	Max	Median (IQR)	Min	Max
C_{min} (ng/mL)	3 (1–5)	0.25	14.8	7 (5–18)	0.82	66.8	9 (8–22)	1.1	81.6
C_{max} (ng/mL)	5 (3–8)	0.89	40.2	14 (9–38)	3.7	138.5	20 (12–51)	4.5	157.8
T_{max} (h)	0.7 (0.5–1)	0	3.03	0.5 (0.5–1)	0	2	0.7 (0.5–1)	0	3.58
$AUC_{0\text{-}3h}$ (ng.h/mL)	11 (7–16)	1.63	63.72	28 (21–84)	5.17	244.23	38 (29–117)	7.23	307.94

$AUC_{0\text{-}3h}$, area under the concentration-time curve from 0 to 3 h; C_{max}, nimodipine maximum concentration; C_{min}, nimodipine trough concentration; T_{max}, time to maximum drug concentration; *, $n = 29$ (one participant who only had two samples collected and was consequently excluded from the pharmacokinetic calculations).

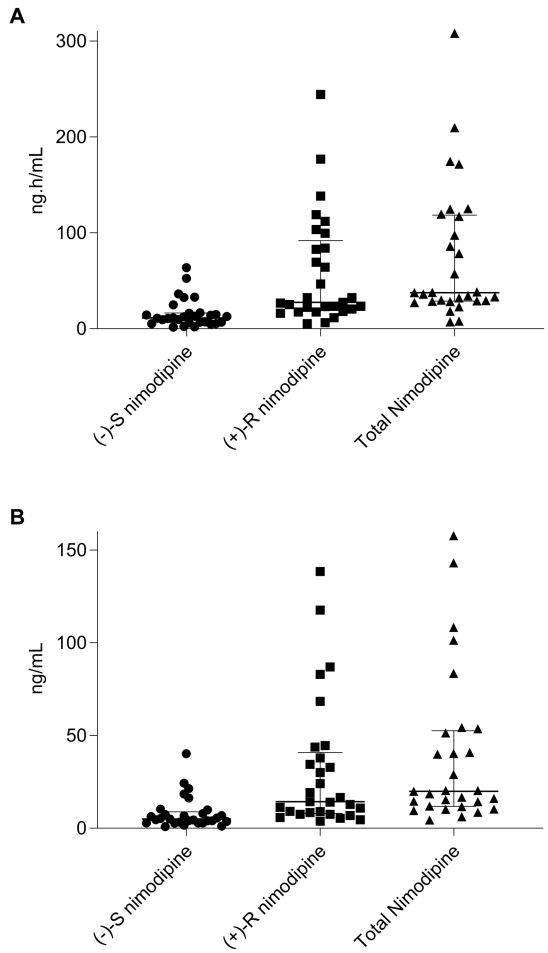

FIGURE 1
Scatter plot and median (interquartile range) of **(A)**, nimodipine area under the concentration-time curve ($AUC_{0\text{-}3h}$) from 0 to 3 h for (–)-S, (+)-R, and total nimodipine; **(B)**, nimodipine maximum concentrations (C_{max}) for (–)-S, (+)-R, and total nimodipine. $n = 29$ (one participant who only had two samples collected and was consequently excluded from the pharmacokinetic calculations).

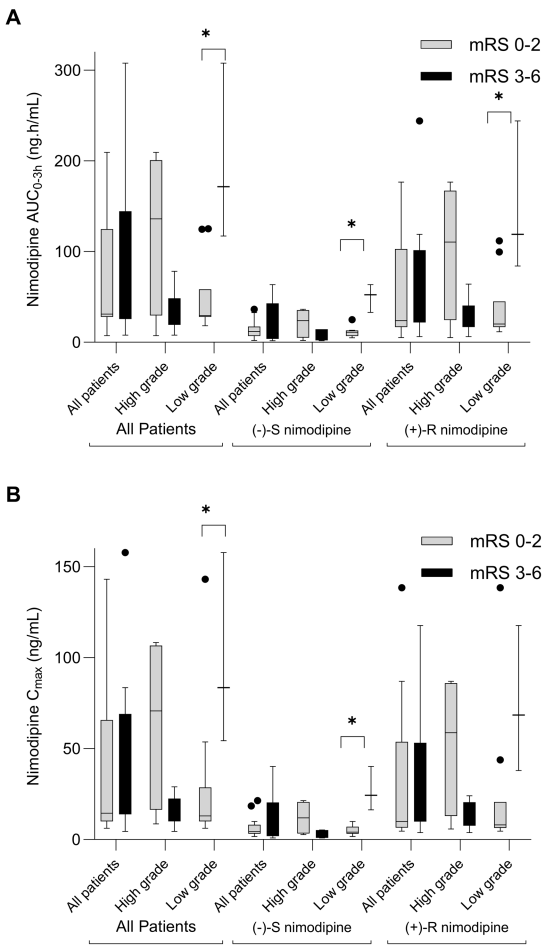

FIGURE 2
Box-plot comparison of nimodipine exposure in aSAH participants who experienced poor outcomes (modified Rankin scale, mRS 3-6) to those who experienced favorable outcomes (mRS 0-2) at 90 days following aSAH. **(A)** $AUC_{0\text{-}3h}$ comparison; **(B)** C_{max} comparison. High grade, World Federation of Neurological Surgeons (WFNS) grade of 3-5; Low Grade, WFNS of 1-2. $n = 23$ (exclusions: 1 lost to follow-up, 1 did not have sufficient samples, and 5 with delayed presentation). *$p < 0.05$.

3.3 Nimodipine exposure and patient outcomes

Nimodipine systemic exposure in aSAH participants who experienced poor outcomes (mRS 3–6) was compared to those who experienced favorable outcomes (mRS 0–2) at 90 days following aSAH. Five participants had delayed presentation exceeding 96 h (time window for nimodipine administration); thus, they were excluded from the comparison. This is because aSAH patients who present with a delay may have different characteristics and outcomes compared to those with immediate or early presentation (37–39). Figure 2 depicts the comparisons of nimodipine $AUC_{0\text{-}3h}$ and C_{max} by mRS at 90 days. As seen in the

figure, $AUC_{0\text{-}3h}$ and C_{max} were not significantly different when the whole cohort was compared. However, when stratified by the admission WFNS grade, a split occurred. Among those who presented with high grade (WFNS 3–5), nimodipine $AUC_{0\text{-}3h}$ in those with favorable outcomes were 4-fold higher than in those with poor outcomes [136(52–192) vs. 33(23–39) ng.h/mL, respectively, value of $p = 0.2$]. Similarly, nimodipine C_{max} in those was favorable outcomes was higher than in those with poor outcomes [71(24–105) vs. 18 (12-20) ng/mL, respectively, value of $p = 0.14$]. Similar findings were observed when individual nimodipine enantiomers were analyzed (Figure 2; Supplementary Tables 1, 2). On the other hand, among those presented with a low grade (WFNS 1–2), nimodipine $AUC_{0\text{-}3h}$ in those with favorable outcomes was significantly lower than in those with poor outcomes [30(28–36) vs. 172(117–308) ng.h/mL, respectively, value of $p = 0.03$]. Similarly, nimodipine C_{max} in those was favorable outcomes was significantly lower than in those with poor outcomes [13(10–20) vs. 84(54–158) ng/mL, respectively, value of $p = 0.03$]. Similar findings were observed when individual nimodipine enantiomers were analyzed (Figure 2; Supplementary Tables 1, 2).

Furthermore, similar results were obtained when the whole cohort, with $AUC_{0\text{-}3h}$, C_{max}, and follow-up data, was analyzed ($n = 28$). $AUC_{0\text{-}3h}$ and C_{max} were not significantly different when the whole cohort was compared [$AUC_{0\text{-}3h}$ (favorable outcome: 34 (29–120) vs. poor outcome: 39 (29–117) ng.h/mL, value of $p = 0.71$); C_{max} (favorable outcome: 17 (10–51) vs. poor outcome: 20 (16–54) ng/mL, value of $p = 0.45$)]. When stratified by admission WFNS grade, a split occurred. Among those presented with high grade (WFNS 3–5), nimodipine $AUC_{0\text{-}3h}$ in those with favorable outcomes was higher than in those with poor outcomes [120(98–175) vs. 33 (23–39) ng.h/mL, respectively, value of $p = 0.1$]. Similarly, nimodipine C_{max} in those with favorable outcomes was significantly higher than in those with poor outcomes [51(40–101) vs. 18 (12–20) ng/mL, respectively, value of $p = 0.07$]. Similar findings were observed when individual nimodipine enantiomers were analyzed. On the other hand, among those presented with a low grade (WFNS 1–2), nimodipine $AUC_{0\text{-}3h}$ in those with favorable outcomes was significantly lower than in those with poor outcomes [33(29–38) vs. 172(117–308) ng.h/mL, respectively, value of $p = 0.02$]. Similarly, nimodipine C_{max} in those with favorable outcomes was significantly lower than in those with poor outcomes [15 (10–20) vs. 84(54–158) ng/mL, respectively, value of $p = 0.02$]. Similar findings were observed when individual nimodipine enantiomers were analyzed.

Nimodipine exposure was also compared between individuals who experienced vasospasm and those who did not (Supplementary Tables 1, 2). All of the comparisons were not statistically different, except for (−)-R and total nimodipine among the participants who presented with high grades. (+)-R nimodipine $AUC_{0\text{-}3h}$ in those who did not develop vasospasm were 4-fold significantly higher than those who had vasospasm [83(64–138) vs. 23 (6–24) ng.h/mL, respectively, value of $p = 0.047$]. Similarly, (−)-R nimodipine C_{max} in those who did not develop vasospasm were 4-fold significantly higher than those who had vasospasm [34(24-83) vs. 9 (6–11) ng/mL, respectively, value of $p = 0.009$]. With regard to DCI, trends of differences in nimodipine exposure were observed, but none reached statistical significance (Supplementary Tables 1, 2). Similar results were obtained when the whole cohort was analyzed.

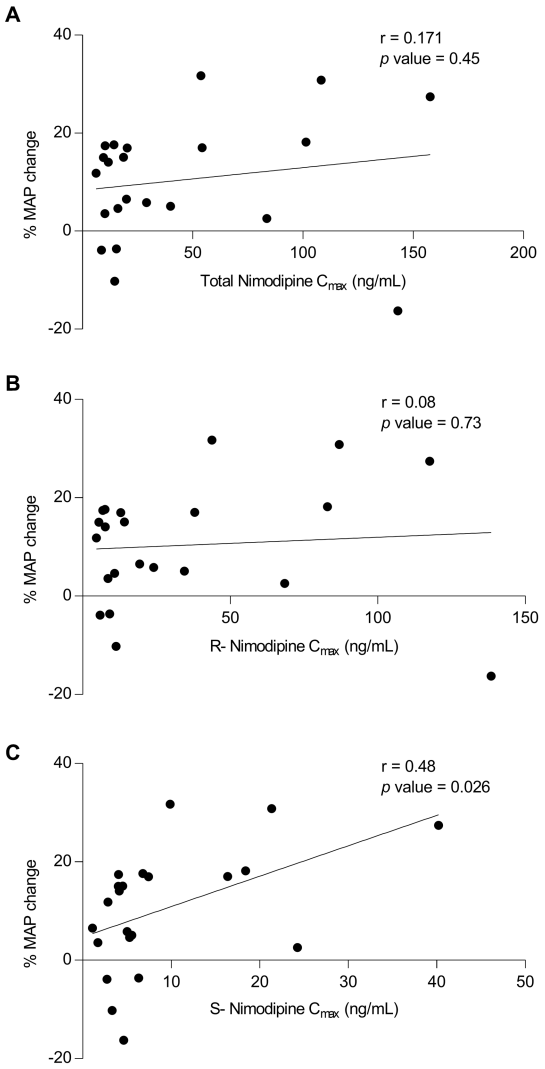

FIGURE 3
Plot of nimodipine maximum concentrations (C_{max}) vs. the percentage mean arterial pressure (MAP) changes following nimodipine administration. **(A)** Total nimodipine; **(B)** (+)-R-enantiomer; **(C)** (−)-S-enantiomer. $n = 22$ included (Excluded participants: 2 were on vasopressors, 2 received intermittent intravenous labetalol concomitantly, 3 did not have MAP data, and 1 did not have C_{max} value).

3.4 Nimodipine exposure and MAP reduction

To determine whether nimodipine enantiomers exhibit differential effects on blood pressure, where hypotension is the main intolerance factor with nimodipine administration, MAP values measured around the sampling nimodipine dose were collected. To avoid the influence of concomitant therapies potentially confounding MAP measurements, those who were concomitantly treated with antihypertensives ($n = 2$, intermittent IV labetalol) and vasopressors ($n = 2$, milrinone and norepinephrine) were excluded from the analysis. Three participants had no MAP data, and one participant did not have a C_{max} value, and therefore, they were excluded. As depicted in Figure 3, there was a significant correlation observed between (−)-S nimodipine alone and the percentage reduction in MAP.

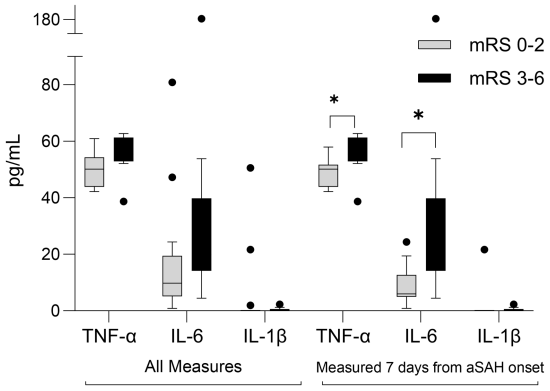

FIGURE 4
Box-plot comparison of inflammatory mediators in aSAH participants who experienced poor outcomes (modified Rankin scale, mRS 3-6) to those who experienced favorable outcomes (mRS 0-2) at 90 days following SAH. All measures ($n = 24$, exclusions: 1 lost to follow-up, 5 delayed presentation); Measured 7-days from aSAH onset ($n = 20$). *$p < 0.05$ IL, interleukin, TNF, tumor necrosis factor.

3.5 Plasma inflammatory markers

Three cytokine plasma levels were measured: IL-6, IL-1β, and TNF-α, three markers potentially implicated with aSAH pathophysiology. Figure 4 summarizes inflammatory mediators' levels among those with favorable and poor mRS outcomes. Excluding those with delayed presentation, plasma TNF-α and IL-6 measured in the first 7 days from SAH onset were significantly elevated in participants with poor mRS at 90 days [TNF-α: 55(54–60) vs. 50(44–52) pg./mL, respectively, value of $p = 0.03$; IL-6: 20(18–26) vs. 6(5–13) pg./mL, respectively, value of $p = 0.02$].

3.6 Covariates potentially associated with nimodipine plasma concentrations

To determine potential covariates associated with nimodipine systemic exposure ($AUC_{0\text{-}3h}$), we explored trends in nimodipine concentrations categorized by different covariates. The explored covariates were age, sex, BMI, WFNS grade, co-administration of phenytoin, inflammatory markers, and nimodipine route of administration (Table 4). Participants with plasma TNF-α levels above 57 pg./mL and those with detectable IL-1β trended toward elevated nimodipine $AUC_{0\text{-}3h}$. Furthermore, there was a trend toward lower nimodipine AUC in those receiving nimodipine enterally via the feeding tube and those concomitantly treated with phenytoin (an LME inducer).

4 Discussion

This was a pilot single-center prospective observational study in adult patients admitted to the University of Alberta Hospital with aSAH. The study is the first to investigate the potential association between nimodipine exposure following oral dosing and patient outcomes. Furthermore, it is the first study to suggest differential effects of individual nimodipine enantiomers, shedding light on the potential utility of individual nimodipine enantiomers.

In the present study, a large variability in nimodipine concentrations was observed (Table 3). Pharmacokinetic studies have reported considerable variability in nimodipine concentrations among aSAH patients, with some individuals showing undetectable levels in their plasma (12–17). For instance, Soppi et al. conducted a study to analyze nimodipine concentrations in patients with aSAH who followed the standard 60 mg oral dose in every 4 h regimen (12). They found that C_{max} was as low as 1 ng/mL to 57 ng/mL in individuals taking tablets, while those receiving an oral suspension exhibited concentrations of 0.9–1.7 ng/mL. Similarly, Abboud et al. compared plasma concentrations of nimodipine between patients who received it parenterally and those who received it orally (16) Among patients who ingested whole nimodipine tablets, the AUC was almost double compared to those who received it through an enteral feeding tube (16). Additionally, two patients with severe SAH exhibited undetectable nimodipine concentrations. The observed variability in nimodipine exposure may be secondary to practice variations in nimodipine administration, systemic inflammation, disease severity, administration of concomitant interacting drugs, and cytochrome P450 polymorphism (17–21). Nevertheless, it is not clear if minimal or lack of systemic exposure to oral nimodipine attenuates the benefit and contributes to worsening patient outcomes.

Following the exclusion of those with delayed presentation, nimodipine $AUC_{0\text{-}3h}$ in participants who experienced poor outcomes (mRS 3-6) was compared to those who experienced favorable outcomes (mRS 0-2) at 90 days following SAH. Among those who presented with high disease severity, nimodipine $AUC_{0\text{-}3h}$ in those with favorable outcomes was 4-fold higher than in those with poor outcomes. On the other hand, among those presented with a low grade (WFNS 1-2), nimodipine $AUC_{0\text{-}3h}$ in those with favorable outcomes was significantly lower than in those with poor outcomes. Similar results were obtained when the whole cohort with follow-up data was analyzed. Although such a finding could be attributed to the small sample size of the study and non-adjustment for confounders, it may suggest the potential increased benefit of nimodipine in those with increased disease severity. A larger multicenter study is needed to determine if such associations persist after controlling for confounders. No previous studies have addressed if an association exists between plasma nimodipine concentrations after oral dosing and clinical outcomes. The study conducted by Riva et al. suggested a link between nimodipine concentrations in cerebrospinal fluid (CSF) and neurological outcomes after 9 months from the onset of aSAH in a group of 23 patients (40). However, they were unable to establish a similar correlation with plasma concentrations. It is worth noting that all patients who received nimodipine through intravenous infusion, resulted in plasma concentrations equal to or greater than 25 ng/mL, which surpasses levels observed in certain patients who received oral doses. Furthermore, determining the association between nimodipine plasma concentration and outcomes might be of greater value than determining CSF concentrations. This is because measuring CSF samples is not practical as not all patients will have readily available CSF.

Nimodipine is a dihydropyridine calcium channel blocker with a chiral carbon atom. The currently marketed compound is a racemic mixture of (+)-R and (−)-S nimodipine. Our study suggested differential effects of individual nimodipine enantiomers, shedding light on the potential utility of individual nimodipine enantiomers. We found that

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TABLE 4 Nimodipine systemic exposure categorized by various covariates.

Covariate		Total $AUC_{0\text{-}3h}$ (ng.h/L)	(−)-S $AUC_{0\text{-}3h}$ (ng.h/L)	(+)-R $AUC_{0\text{-}3h}$ (ng.h/L)
Age (years)	<60 ($n = 15$)	37 28–125)	11 (6–15)	32 (17–112)
	≥60 ($n = 14$)	37 (29–117)	14 (7–17)	27 (23–84)
Sex	Males ($n = 12$)	33 (28–107)	9 (6–20)	26 (20–84)
	Females ($n = 17$)	38 (29–120)	13 (9–16)	33 (21–103)
BMI (kg/m^2)	<18.5 ($n = 2$)	35 (32–38)	6 (5–7)	29 (25–33)
	18.5 - < 25 ($n = 11$)	29 (27–120)	11 (5–16)	23 (18–103)
	25 - < 30 ($n = 6$)	58 (33–98)	12 (6–15)	48 (23–83)
	≥30 ($n = 10$)	62 (30–125)	14 (11–33)	48 (17–112)
Phenytoin co-administration	Phenytoin ($n = 4$)	33 (26–68)	10 (4–15)	23 (22–53)
	No Phenytoin ($n = 25$)	38 (29–120)	11 (7–17)	32 (18–100)
WFNS grade	High grade ($n = 11$)	39 (23–120)	14 (2–16)	32 (21–103)
	Low grade ($n = 18$)	35 (29–117)	11 (7–16)	27 (18–84)
Route of administration	Oral ($n = 23$)	38 (29–120)	11 (7–17)	32 (18–100)
	Enteral via FT ($n = 6$)	33 (23–78)	10 (2–14)	23 (21–64)
TNF-α (pg/mL)	<45 ($n = 8$)	36 (23–91)	8 (6–18)	28 (17–73)
	45–52 ($n = 7$)	34 (29–120)	13 (11–16)	28 (17–103)
	53–57 ($n = 7$)	36 (29–78)	9 (5–14)	26 (23–64)
	>57 ($n = 7$)	86 (28–210)	17 (53–5)	69 (21–177)
IL-6 (pg/mL)	<6.0 ($n = 8$)	33 (29–106)	12 (10–15)	24 (18–91)
	6.0–15 ($n = 7$)	38 (27–98)	13 (5–15)	33 (17–83)
	16–30 ($n = 7$)	29 (8–125)	5 (2–33)	23 (6–100)
	>30 ($n = 7$)	39 (36–120)	11 (7–16)	32 (27–103)
IL-1β (pg/mL)	0 ($n = 23$)	34 (28–86)	11 (5–14)	25 (17–69)
	>0 ($n = 6$)	107 (39–120)	16 (10–33)	84 (32–103)

Data are presented as median (interquartile range). $AUC_{0\text{-}3h}$, area under the concentration-time curve from 0 to 3 h; BMI, body mass index, IL, interleukin; TNF, tumor necrosis factor; WFNS, World Federation of Neurological Surgeons. High grade, World Federation of Neurological Surgeons (WFNS) grade of 3-5; Low Grade, WFNS of 1-2. Cytokine ranges represent quantiles that were generated using STATA. $n = 29$ (one participant who only had two samples collected and was consequently excluded from the pharmacokinetic calculations).

that among those who presented with severe disease, $AUC_{0\text{-}3h}$ of (+)-R nimodipine in those who did not develop vasospasm was 4-fold significantly higher than in those who had vasospasm. Such a difference was not apparent with (−)-S nimodipine. On the other hand, our data suggested that (−)-S but not (+)-R nimodipine concentrations were correlated with percent MAP reduction ($r = 0.48$, value of $p = 0.03$), and the (−)-S enantiomer could be the culprit for the observed nimodipine-induced hypotension, which is the main challenge limiting the dosing of nimodipine (41). Towart et al. discovered that (−)-S nimodipine exhibits approximately double the potency as a vasorelaxant compared to the racemic mixture, supporting our finding of such differential pharmacology (42). In addition, in our study, (−)-S nimodipine plasma concentrations were approximately 4-fold lower than the (+)-R enantiomer. Enantioselective first-pass metabolism leads to a more rapid elimination of the (−)-S enantiomer compared to the (+)-R enantiomer after oral administration (20, 43–45). However, such differential effects were not obvious when nimodipine was given intravenously, resulting in higher concentrations of the (−)-S enantiomer compared to oral dosing. This could potentially explain, at least in part, the excessive hypotensive effect reported following the IV route (46). These findings, although preliminary, are hypothesis generating, suggesting that using (+)-R nimodipine instead of the racemic mixture could potentially retain the benefits of racemic nimodipine while reducing its hypotensive effect, a main limiting factor of nimodipine therapy. Hypotension should be avoided to avoid cerebral hypoperfusion and complications following aSAH (2, 46). Further studies are needed to investigate this hypothesis.

In order to identify potential covariates associated with nimodipine systemic exposure, we examined trends in nimodipine concentrations categorized by various covariates (Table 4). Participants with plasma TNF-α levels above 57 pg./mL and those with detectable IL-1β tended toward elevated nimodipine exposure. This was similar to the findings of an earlier study conducted by S.H.M. where systemic inflammation resulted in significantly increased concentrations of the calcium channel blocker (CCB) verapamil (47–49). This has been attributed to inflammation-induced downregulation of cytochrome P450 enzymes and increased verapamil protein binding (47, 49–51). However, despite the increased concentrations, verapamil's pharmacological effect was compromised secondary to inflammation-induced downregulation of L-type calcium channels, verapamil's target receptor (47, 49, 52). Similarly, the pharmacological response to nifedipine was also compromised in the setting of inflammation (53, 54). It is not known,

however, if these inflammation-induced alterations result in reduced nimodipine effects as seen with other CCBs. In the present study, plasma TNF-α and IL-6 measured in the first 7 days from SAH onset were elevated in participants with poor mRS at 90 days. This was similar to several articles reporting an association between increased systemic inflammation and poor outcomes following aSAH (34–36, 55, 56). However, none investigated if the observed poor outcomes could be attributed, at least in part, due to altered nimodipine actions and disposition. Further studies are needed.

Furthermore, there was a trend toward lower nimodipine $AUC_{0\text{-}3h}$ in those receiving nimodipine enterally via the feeding tube and those concomitantly treated with phenytoin (an LME inducer). We previously reported an association between the nimodipine administration technique and patient outcomes where patients receiving crushed nimodipine tablets enterally had worse outcomes compared to those who received whole tablets after controlling for disease severity (57). We confirmed such findings in a multicenter retrospective study where we compared various enteral administration formulations and techniques (22). This could be attributed to the reduced oral bioavailability of enteral nimodipine, especially the manufacturer recommends against tablet crushing due to the risk of reduced absorption (58).

Our study was limited by the small sample size. We were unable to control confounders associated with the tested outcomes in multivariate analysis. Moreover, it is crucial to exercise caution when interpreting our results primarily due to the presence of contradictory findings related to our primary research question. This situation heightens the risk of confirmation bias influencing our conclusions. Although the study was not powered to detect differences, it was meant to identify trends that will potentially be utilized to design a larger multicenter study.

5 Conclusion

aSAH is a severe medical crisis requiring urgent medical and surgical attention. The demonstrated advantages of administering nimodipine in aSAH underscore the importance of providing it to all patients, as long as it is well tolerated. An individualized approach to the administration of nimodipine remains an area of ongoing research as the association between variations in pharmacokinetic parameters and clinical outcomes remains unclear. The findings of this research aimed to pave the way for further research to determine whether nimodipine exposure is an independent predictor of aSAH outcomes and ways to optimize the dosing of nimodipine in aSAH to possibly increase the likelihood of achieving pharmacokinetic measures associated with treatment success and improved patients' clinical 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 humans were approved by the Health Research Ethics Board of the University of Alberta. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SM: conceptualization, supervision, project administration, study design, statistical analysis, writing original draft, manuscript revision, and data interpretation. FH: data acquisition, writing review, and data interpretation. FI: data acquisition, writing review, and data interpretation. SF: data acquisition, writing review, and data interpretation. SL: data acquisition and writing review. CO'K: study design and writing review. JK: study design and writing review. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1233267/full#supplementary-material

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Factors affecting 30-day mortality in poor-grade aneurysmal subarachnoid hemorrhage: a 10-year single-center experience

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Background: The management of patients with poor-grade aneurysmal subarachnoid hemorrhage (aSAH) is burdened by an unfavorable prognosis even with aggressive treatment. The aim of the present study is to investigate the risk factors affecting 30-day mortality in poor-grade aSAH patients.

Methods: We performed a retrospective analysis of a prospectively collected database of poor-grade aSAH patients (World Federation of Neurosurgical Societies, WFNS, grades IV and V) treated at our institution from December 2010 to December 2020. For all variables, percentages of frequency distributions were analyzed. Contingency tables (Chi-squared test) were used to assess the association between categorical variables and outcomes in the univariable analysis. Multivariable analysis was performed by using the multiple logistic regression method to estimate the odds ratio (OR) for 30-day mortality.

Results: A total of 149 patients were included of which 32% had WFNS grade 4 and 68% had WFNS grade 5. The overall 1-month mortality rate was 21%. On univariable analysis, five variables were found to be associated with the likelihood of death, including intraventricular hemorrhage (IVH $\geq$ 50 mL, $p = 0.005$), the total amount of intraventricular and intraparenchymal hemorrhage (IVH + ICH $\geq$ 90 mL, $p = 0.019$), the IVH Ratio (IVH Ratio $\geq$ 40%, $p = 0.003$), posterior circulation aneurysms ($p = 0.019$), presence of spot sign on initial CT scan angiography ($p = 0.015$).

Nonetheless, when the multivariable analysis was performed, only IVH Ratio ($p = 0.005$; OR 3.97), posterior circulation aneurysms ($p = 0.008$; OR 4.05) and spot sign ($p = 0.022$; OR 6.87) turned out to be independent predictors of 30-day mortality.

Conclusion: The risk of mortality in poor-grade aSAH remains considerable despite maximal treatment. Notwithstanding the limitations of a retrospective study, our report highlights some neuroradiological features that in the emergency setting, combined with leading clinical and anamnestic parameters,

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may support the multidisciplinary team in the difficult decision-making process and communication with family members from the earliest stages of poor-grade aSAH. Further prospective studies are warranted.

KEYWORDS

poor-grade, subarachnoid hemorrhage, predictors, Mortality, intracranial aneurysms

Introduction

Aneurismal subarachnoid hemorrhage (aSAH) remains a detrimental condition despite advances in treatment. Patients with poor clinical status (World Federation of Neurosurgical Societies WFNS IV and V) represent approximately 20 and 40% (1) of hospitalized aSAH patients, respectively, and have a significant overall mortality rate, ranging from 26 to 43% (2), and an unfavorable clinical outcome. For these reasons, patients with poor-grade aSAH have often been considered for withdrawal of life-saving equipment based on the prognostication from the initial neurological assessment. Over the past 20 years, exceptional advances in diagnostic imaging (computed tomography CT, CT angiography, Digital Subtraction Angiography DSA) and treatment (surgical, endovascular and neurocritical care) have not yet shifted the paradigm toward significantly better clinical outcomes.

In this scenario, we would need simple parameters to support the decision-making process and identify patients who harbor a higher probability of survival from this acute event.

The hemorrhagic burden, with its subarachnoid, intraventricular and intraparenchymal counterparts, has been associated with the development of delayed cerebral ischemia (3, 4) and the severity of subarachnoid hemorrhage (5, 6). For these reasons, among many others, radiological parameters, especially in the early phases of the acute event, could be investigated as outcome prognosticators.

The aim of the present study is to investigate the baseline risk factors (clinical, radiological and laboratory) as independent outcome predictors of 30-day mortality in patients with poor-grade aSAH.

Materials and methods

Study design and setting

We retrospectively reviewed the clinical, treatment (surgical and endovascular) and outcome (30-day mortality) data of patients with poor-grade aSAH treated at our institution (IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy) from December 2010 to December 2020.

Participants and study size

All patients treated in the early phase were retrospectively reviewed. The eligibility criteria included (a) aSAH with WFNS IV or V on admission after stabilization of vital parameters (7), (b) age of ≥18 years, and (c) treatment within 24 h of hospital admission. Patients with (a) out-of-hospital cardiac arrest (8, 9), (b) traumatic, mycotic or arteriovenous malformation-related aneurysms, (c) clinical signs of severe brainstem dysfunction (bilaterally dilated pupils, no corneal reflexes), (d) pregnancy, were excluded from this analysis.

For all patients, family members signed an informed consent for the scientific use of the data according to the requirements of the local Institutional Review Board.

Data sources

Clinical and treatment data were collected in a digital archive. Follow-up information was obtained by trained personnel, blinded to the results of the present study during outpatient clinical evaluations or telephone interviews with patients, their relatives, or their general practitioners at 1 month after surgery.

Treatment protocol

The treatment protocol has been described in part elsewhere (10). As per our Institutional protocol we offer treatment to all poor-grade aSAH patients in the early (24 h) phase after hospital admission, except some with clinical signs of severe brainstem dysfunction. This strategy is conducted for the purpose of preventing aneurysm rebleeding. The neurocritical and early treatment strategy was in agreement with the international aSAH guidelines published at the time of the last patient recruitment (11, 12).

Briefly, all patients included in this study were centralized at our Institution after early stabilization of vital parameters. If acute hydrocephalus was present on the initial CT scan, an external ventricular drainage (EVD) was placed prior to aneurysm treatment. All patients underwent early CT angiography and multidisciplinary discussion (with at least one senior Interventional Neuroradiologist, one senior Vascular Neurosurgeon and one senior Neuroanesthesiologist with experience in aSAH management) of the indication and type of treatment based on clinical condition, comorbidities, and angioarchitectural features of the aneurysm. For patients whose aneurysms were amenable to either endovascular or surgical treatment, coiling was identified as the preferred treatment modality. Diagnostic DSA was performed in patients who did not reveal an aneurysm on CT angiography, or to identify and characterize perforating arterial branches from the aneurysmal neck before surgery, or, in any case, before planned endovascular treatment as part of the procedure.

Neurocritical care, prevention and treatment of vasospasm and delayed cerebral ischemia (DCI) were provided to all patients included in the study according to guidelines (11, 12).

The effectiveness of aneurysm treatment was investigated by postoperative CT angiography or DSA (in selected challenging cases)

for surgically treated patients and with magnetic resonance angiography (MRA) for those patients who received endovascular treatment.

Patients who developed symptomatic radiologic hydrocephalus, in the subacute phase after EVD removal, underwent ventriculo-peritoneal (VP) shunt placement.

Assessment quantitative variables and outcome

We collected demographic data (age, sex), clinical and laboratory data before treatment (including on admission WFNS grade stabilization of vital parameters, mean arterial blood pressure MAP, presence of seizure at symptom onset, serum glucose level, PaO_2/FiO_2 Ratio for respiratory failure, presence of antiplatelet/anticoagulant use, presence of pupillary light reflex PLR, white blood cell count WGC), radiological parameters on initial CT scan and CT angiography, CTA (modified Fisher scale mFS, number and type of ventricles filled with blood, presence of intraventricular hemorrhage IVH, IVH volume, presence of intraparenchymal hemorrhage ICH, ICH volume, total amount of ICH + IVH, IVH ratio calculated as [IVH/ (total amount of ICH + IVH)], presence of acute hydrocephalus, presence of midline shift, presence of subdural or extradural hematoma, location of aneurysm, presence of spot sign on CTA, any involvement of the parental arteries in the aneurysmal neck), treatment-related parameters (time from symptom onset to treatment, type of treatment, placement of external ventricular drainage EVD), presence of rebleeding at any time (before or after treatment), complications (delayed cerebral ischemia (13), hydrocephalus requiring permanent shunt placement).

Detailed volumetric assessment of intracranial hemorrhage, semi-automated segmentation and volumetric assessment were performed on non-contrast enhanced brain CT scans by two different neuro-radiologists blinded to patient characteristics and outcome. The neuroradiological analysis was carried out using the Advantage Workstation (AW) Server 3.2 (GE Healthcare, Chicago, Illinois, United States). Bleeding volumes were calculated in milliliters for the ICH and the IVH counterparts by multiplying the slice thickness by the hemorrhagic region. The IVH ratio was calculated as [IVH /total amount of ICH + IVH] and expressed as a percentage. Clinical outcome was defined as mortality at 1 month.

Statistical analysis

For all pre-treatment (demographic, clinical and laboratory data), radiological, and treatment-related parameters, rebleeding and complications, percentages of frequency distributions were analyzed. For statistical analysis, variables were sorted as indicated below. Variables were transformed into binary variables to be used in the univariable and multivariable analyses. The dichotomous variables were sex, WFNS grade, seizure, antiplatelet/anticoagulant, presence of PLR, presence of IVH, presence of ICH, acute hydrocephalus, midline shift, subdural/extradural hematoma, spot sign, involvement of the parental arteries in the aneurysm neck, type of treatment, EVD, rebleeding, delayed cerebral ischemia, and shunt placement. For non-dichotomous variables, cut-off values were chosen according to clinical/radiological criteria and published data. Subsets for predictors and outcome variables were as follows: age, < 65 years Vs. ≥ 65 years; MAP, < 90 mmHg Vs. ≥ 90 mmHg; serum glucose level, <180 mg/dL Vs. ≥ 180 mg/dL; PaO_2/FiO_2 Ratio, < 200 Vs. ≥ 200; WGC, $< 15 \times 10^9 \geq 15 \times 10^9$/L; mFS, 3 Vs. 4; number of ventricles filled with blood, < 3 Vs. ≥ 3; IVH volume, < 50 cc Vs. ≥ 50 mL; ICH volume, < 30 cc Vs. ≥ 30 mL; ICH + IVH volume, < 90 cc Vs. ≥ 90 mL; IVH ratio, < 40% Vs. ≥ 40%; aneurysm location, anterior circulation Vs. posterior circulation; time from symptom onset to treatment, < 6 h Vs. ≥ 6 h.

For univariable analysis, contingency tables and Pearson's Chi-squared test were used to evaluate the association between the categorical variables and the outcome. Results were presented as absolute (n) and relative frequencies (%). Multivariable analysis was performed using the step-wise logistic regression model, including only variables that were statistically significant in the univariable analysis. Results were presented as Odds Ratio (OR) and 95% Confidence Interval (95% CI). Statistical significance was defined as a p value <0.05. Statistical analysis was performed using Stata 14.2.

Results

Participants and descriptive data

A total of 149 patients with poor-grade aSAH were included in this study. None of the patients in this series presented with an in-hospital cardiac arrest. The mean age was 61.3 (SD 11.9 years). In total, 47 patients (32%) presented with WFNS grade 4 and 102 patients (68%) with WFNS grade V. A total of 126 patients (85%) harbored an aneurysm located in the anterior circulation and 23 patients (15%) in the posterior circulation. A total of 99 patients (66%) were treated surgically while endovascular treatment was performed in 50 cases (44%). The overall rebleeding rate (at any time, before and after treatment) was 11%.

Tables 1, 2 summarize the clinical/laboratory variables on admission and the radiological parameters analyzed.

A total of 126 patients (85%) presented with IVH on the initial CT scan and 111 patients (74%) presented with acute hydrocephalus requiring emergent EVD placement. In total, 107 patients (72%) had some degree of ICH on the admission CT scan. Among radiological variables, the mean volumes of IVH, ICH and the total amount of IVH + ICH were 17.5 (SD 24.7) mL, 18.6 (SD 23.6) mL, and 36.1 (SD 32.6) mL, respectively. The mean IVH ratio was 49.4 (SD 40.6) %.

Main results, outcome data and predictors of 30-day mortality

The overall mortality rate at 1 month after poor-grade aSAH was 21%. The causes of mortality were related to the aSAH or complications related to the aSAH in all cases. In total, 59 patients (40%) presented with delayed cerebral ischemia and 51 patients (34%) developed hydrocephalus during the follow-up period (1 month), requiring ventriculo-peritoneal placement. Of the 32 patients (21% of the total) who presented with pupillary reflex abnormalities on admission, 9 patients (6%) did not resolve after aneurysm treatment and they were non-survivors at 1 month after aSAH.

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TABLE 1 Clinical and laboratory features on admission.

Clinical and laboratory variables	No. of patients (%)	Survivors	Non-survivors
Sex			
Male subjects	41 (28%)	33 (30%)	8 (26%)
Female subjects	108 (72%)	85 (70%)	23 (74%)
WFNS score			
IV	47 (32%)	39 (33%)	8 (26%)
V	102 (68%)	79 (67%)	23 (74%)
Seizure presentation			
No	138 (93%)	107 (91%)	31 (100%)
Yes	11 (7%)	11 (9%)	0
Onset of neurological deficits			
No	88 (59%)	66 (56%)	22 (71%)
Yes	61 (41%)	52 (44%)	9 (29%)
Pupillary reflex			
Normal	117 (79%)	95 (81%)	22 (71%)
Abnormal	32 (21%)	23 (19%)	9 (29%)
Mean Arterial Blood Pressure (MAP)			
< 90 mmHg	116 (78%)	90 (76%)	26 (84%)
≥ 90 mmHg	33 (22%)	28 (24%)	5 (16%)
Glycemia			
< 180 mg/dL	90 (60%)	77 (65%)	13 (42%)
≥ 180 mg/dL	59 (40%)	41 (35%)	18 (58%)
White Blood Cell (WBC) count			
$< 15 \times 10^9$/L	93 (62%)	79 (67%)	14 (45%)
$\geq 15 \times 10^9$/L	56 (38%)	39 (33%)	17 (55%)
PaO_2/FiO_2 (P/F) ratio			
≥ 200	117 (79%)	94 (80%)	23 (74%)
< 200	32 (21%)	24 (20%)	8 (26%)
Anticoagulant therapy			
No	146 (98%)	116 (98%)	30 (97%)
Yes	3 (2%)	2 (2%)	1 (3%)
Antiplatelet therapy			
No	121 (81%)	97 (82%)	24 (77%)
Yes	28 (19%)	21 (18%)	7 (23%)

WFNS, World Federation of Neurosurgical Societies.

The univariable statistical analysis identified five variables associated with the likelihood of death. The mortality rate was higher in patients harboring a posterior circulation aneurysm in comparison with patients with anterior circulation aneurysms (39% Vs. 17%, $p = 0.019$). On the initial CTA a spot sign emerged in 7 patients (5%), of whom 57% were dead at 1 month and 43% were alive ($p = 0.015$). Investigating the quantitative radiological analysis, IVH volume ≥ 50 mL ($p = 0.005$), IVH + ICH volume ≥ 90 mL ($p = 0.019$), and IVH Ratio ≥ 40% ($p = 0.003$) were revealed to be associated with mortality at 1 month. Figures 1–5

TABLE 2 Radiological parameters.

Radiological variables	Total (149 patients)	Survivors (118 patients)	Non-survivors (31 patients)
mFISHER scale			
3	23 (15%)	21 (18%)	2 (6%)
4	126 (85%)	97 (82%)	29 (94%)
IVH volume			
< 50 mL	132 (89%)	109 (92%)	23 (74%)
≥ 50 mL	17 (11%)	9 (8%)	8 (26%)
ICH volume			
< 30 mL	112 (75%)	86 (73%)	26 (84%)
≥ 30 mL	37 (25%)	32 (27%)	5 (16%)
ICH + IVH total volume			
< 90 mL	139 (93%)	113 (96%)	26 (84%)
≥ 90 mL	10 (7%)	5 (4%)	5 (16%)
IVH Ratio			
< 40%	69 (46%)	62 (53%)	7 (23%)
≥ 40%	80 (54%)	56 (47%)	24 (77%)
Number of ventricles filled with blood			
< 3	46 (31%)	39 (33%)	7 (23%)
≥ 3	103 (69%)	79 (67%)	24 (77%)
Type of IVH			
Monoventricular	10 (8%)	8 (8%)	2 (7%)
Biventricular	12 (10%)	12 (12%)	0
Triventricular	11 (9%)	7 (7%)	3 (10%)
Tetraventricular	33 (26%)	26 (26%)	7 (24%)
Acute hydrocephalus			
No	38 (26%)	29 (25%)	9 (29%)
Yes	111 (74%)	89 (75%)	22 (71%)
Midline shift			
< 5 mm	98 (66%)	81 (69%)	17 (55%)
≥ 5 mm	51 (34%)	37 (31%)	14 (45%)
Subdural / extradural hematoma			
No	120 (81%)	93 (79%)	27 (87%)
Yes	29 (19%)	25 (21%)	4 (13%)
Aneurysm location			
Anterior circulation	126 (85%)	104 (88%)	22 (71%)
Posterior circulation	23 (15%)	14 (12%)	9 (29%)
Spot sign			
No	142 (95%)	115 (97%)	27 (87%)
Yes	7 (5%)	3 (3%)	4 (13%)
Vessel involvement in aneurysmal neck			
No	114 (77%)	90 (76%)	24 (77%)
Yes	35 (23%)	28 (24%)	7 (23%)

IVH, Intraventricular Hemorrhage. ICH, Intraparenchymal Hemorrhage. IVH Ratio, [IVH / (IVH + ICH)].

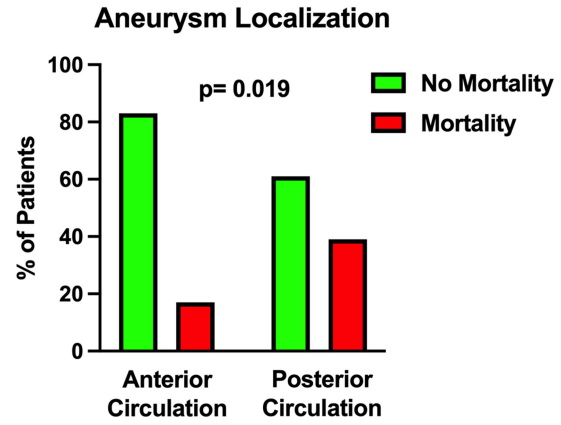

FIGURE 1
Univariable analysis showing the correlation between posterior circulation aneurysm location and mortality.

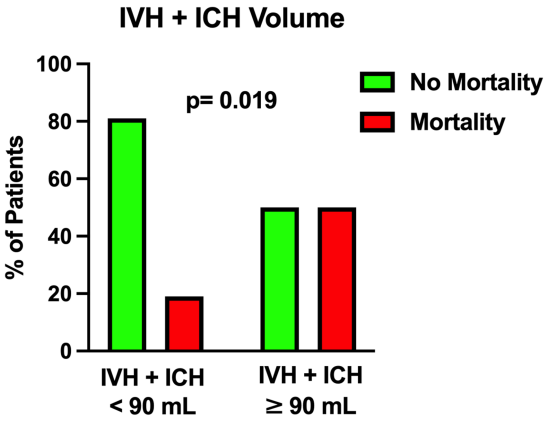

FIGURE 4
Univariable analysis showing the correlation between the total amount of intraventricular hemorrhage and intraparenchymal hemorrhage volume and mortality.

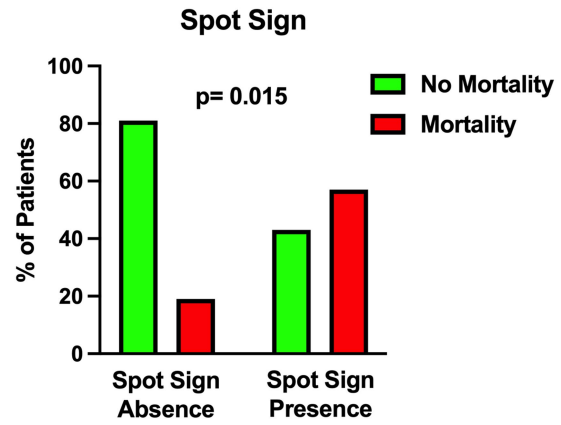

FIGURE 2
Univariable analysis showing the correlation between spot sign presence and mortality.

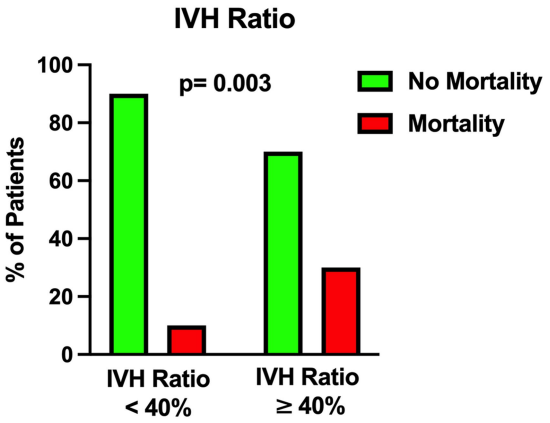

FIGURE 5
Univariable analysis showing the correlation between intraventricular hemorrhage ratio (see the text) and mortality.

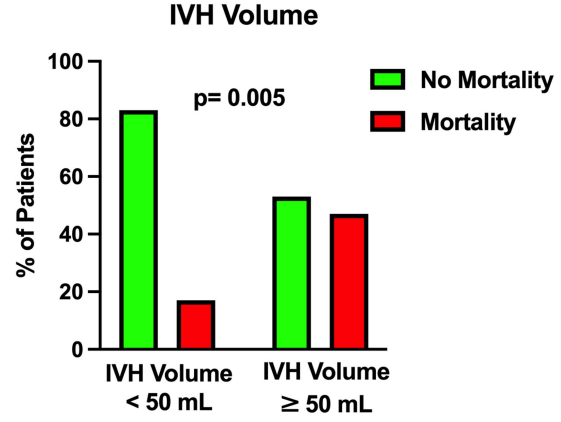

FIGURE 3
Univariable analysis showing the correlation between intraventricular hemorrhage volume and mortality.

depict the results of the univariable analysis for variables that were found to be significant.

Nonetheless, when multivariable analysis was performed, only IVH Ratio ≥ 40% ($p = 0.005$; OR 3.97; 95% CI 1.52–10.36), posterior circulation aneurysms ($p = 0.008$; OR 4.05; 95% CI 1.44–11.37) and spot sign presence ($p = 0.022$; OR 6.87; 95% CI 1.32–35.88) turned out to be independent predictors of 30-day mortality (Table 3). A case example is illustrated in Figure 6.

Discussion

Key results

In this single-center retrospective study, we investigated the predictors of 30-day mortality in a series of patients with poor-grade aSAH treated surgically or endovascularly over one decade.

Our analysis revealed that the ratio of IVH volume to the total amount of IVH and ICH counterparts ("IVH ratio"), the presence of a spot sign on the initial CTA and the localization of the aneurysm in the posterior circulation were strongly associated with the occurrence of mortality within 1 month after the acute event.

TABLE 3 Multivariable logistic model using 30-day mortality as the outcome.

30-day mortality	Odds ratio	*p*	95% confidence interval
IVH ratio ≥ 40% vs. < 40%	3.97	0.005	1.52–10.36
Posterior circulation vs. anterior circulation aneurysm	4.05	0.008	1.44–11.37
Spot sign presence vs. absence	6.87	0.022	1.32–35.88

IVH, Intraventricular Hemorrhage.

Interpretation

In the field of cerebrovascular disease, poor-grade aSAH accounts for a large percentage of neurological disability and, consequently, a high burden on the community and the patient's caregivers (2, 14, 15).

In the literature, different reports and scores (16, 17) have addressed the factors influencing good and poor outcomes in aSAH and, in recent years, some studies have specifically considered the subset of poor-grade aSAH patients.

Notably, in 2022 de Winkel et al. published a systematic review and meta-analysis (18) on early predictors of functional outcome in poor-grade aSAH. This analysis revealed that WFNS grade or Hunt and Hess (HH) grade IV, presence of clinical improvement before aneurysm treatment and intact pupillary light reflex were associated with the likelihood of favorable outcome, while, older age, increasing modified Fisher grade and the presence of intracerebral hematoma on admission imaging decreased the possibility of favorable outcome (18). Moreover, in 2021 Shen et al. (2) identified a scoring model to predict functional outcomes in poor-grade aSAH including different significant predictors

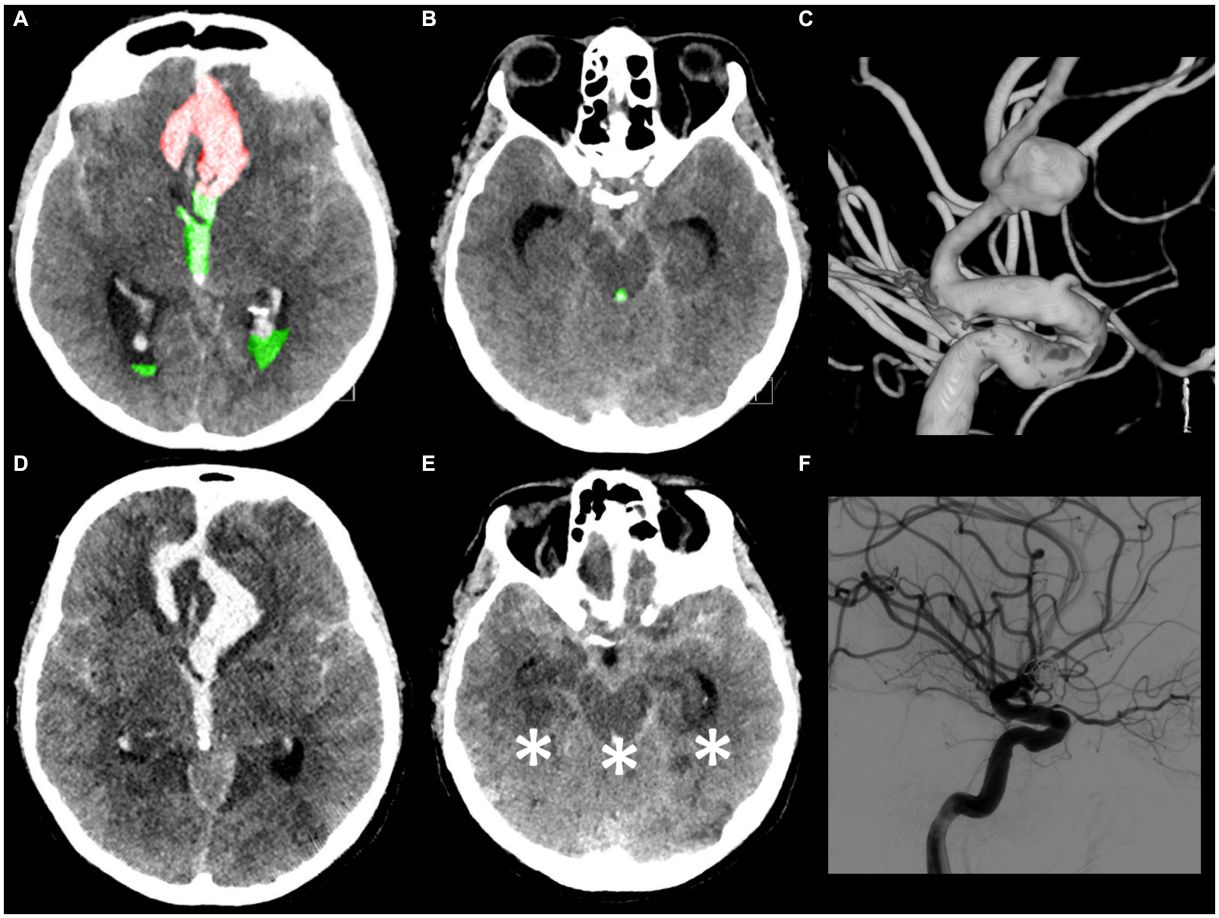

FIGURE 6
A 53-year-old male patient presented with a loss of consciousness. The WFNS score evaluation on admission was V with isochoric pupils and an intact pupillary light reflex. The initial CT scan **(A,B)** demonstrated the presence of a mFisher grade 4 aSAH with intraventricular hemorrhage (green **A,B**), volume 30 mL, and acute hydrocephalus with intraparenchymal hemorrhage (red **A**), volume 7 mL (IVH ratio 81%). The CT angiography and digital subtraction angiography **(C)** showed a ruptured communicating artery aneurysm. An urgent external ventricular drainage was placed and the aneurysm was endovascularly treated within 5 h of symptom onset. The 72 h post-treatment CT scan (**D,E** in corresponding slices as compared, respectively, with **A,B**) revealed the presence of bilateral temporal ischemia, occipital ischemia, and pontomesencephalic ischemia (asterisk **E**). **(F)** Post-coiling digital subtraction angiography showing aneurysm occlusion. The patient died 5 days after aSAH.

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TABLE 4 Literature review of mortality predictors in patients with poor-grade aneurysmal subarachnoid hemorrhage.

First author and year	No. pts	Population	Treatment (%)	IVH (%)	ICH (%)	Mortality rate	Factors affecting mortality
Yoshimoto et al., 1997	68	WFNS IV (56%) or WFNS V (44%)	No treatment (40%) NCH (60%)	NA§	NA§	50% at discharge	Unreactive pupils on admission No motor response on admission
Szklener et al., 2015	101	WFNS IV (26%) or WFNS V (74%)	No treatment (100%)	63%	NA§	73% at 1 month	WFNS grade, Age, Fisher grade, Leukocytosis
van Lieshout et al., 2016	61	WFNS V	NA§	NA§	NA§	28% in-hospital mortality	Delayed transport to specialized neurosurgical care Cardiovascular complications
Cai et al., 2017	58	WFNS IV (70,2%) or WFNS V (29,8%)	NRD (100%)	46%	NA§	27% at 6 months	Hunt-Hess grade, Age, Fisher grade, Systolic blood pressure variability-successive variation
Panni et al., 2019	63	WFNS IV (44,4%) or WFNS V (55,6%)	NCH (31,7%) NRD (68,3%)	82,5%	NA§	30,2% at 12 months	Higher volume of global intracranial bleeding (cutoff 51 mL), the presence of global cerebral edema on admission CT scan
Xie et al., 2019	66	HH IV (58%) or HH V (42%)	NCH (100%)	74%	46%	27% at 6 months	HH grade V ($p = 0,04$) Admission serum fibrinogen level ($p = 0,006$)
Lashkaret al., 2020	176	HH V	No treatment (36%) NCH (32,9%) NRD (31,1%)	79,1%	52,5%	65,8% at 12 months	Older age No treatment
Gouvêa Bogossian et al., 2021	353	WFNS IV (32%) or WFNS V (68%)	NA§	94%	NA§	57% in-hospital mortality	Age, SOFA Score, WFNS 5, Endovascular treatment, Prophylactic nimodipine, Intracranial hypertension, Hydrocephalus
Duan et al., 2022	116	WFNS IV (35%) or WFNS V (65%)	NCH (100%)	96,3%	NA§	35% in-hospital mortality	Age ≥ 65 years, pupillary changes, delayed cerebral ischemia, use of Subarachnoid Hemorrhage Early Brain Edema Score for management of decompressive craniectomy
Present study	149	WFNS IV (32%) or WFNS V (68%)	NCH (66%) NRD (44%)	85%	72%	21% at 1 month	IVH Ratio ≥ 40% ($p < 0,005$) Posterior circulation aneurysms ($p < 0,008$) Spot Sign presence ($p < 0,022$)

pts, patients; IVH, Intraventricular Hemorrhage; ICH, Intraparenchymal Hemorrhage; SAH, Subarachnoid Hemorrhage; WFNS, World Federation of Neurosurgical Societies; HH grade, Hunt-Hess grade; NCH, Neurosurgical Treatment; NRD, Neuroradiological Treatment; SOFA, Sequential Organ Failure Assessment; NA: Not Available.

(modified Fisher grade > 2, age ≥ 65 years, conservative treatment, WFNS grade V, delayed cerebral ischemia, shunt-dependent hydrocephalus and cerebral herniation) for poor prognosis (modified Rankin Scale ≥3). According to this score model, patients were divided into three categories: low risk (0–1 points), intermediate risk (2–3 points), and high risk (4–9 points), with predicted risks of poor prognosis of 11, 52, and 87%, respectively (2).

As a matter of fact, notwithstanding the advancements in techniques and management that ideally allow for intensive and adequate treatment, the mortality and morbidity rates in patients with poor-grade aSAH remain very high. The decision-making process during the early phases of an acute cerebrovascular event is arduous and the proper indication to treat and resource distribution results are very challenging.

Few studies have focused on the factors affecting mortality in poor-grade aSAH. Table 4 summarizes the results of the most relevant reports highlighting this specific focus (1, 5, 15, 19–24).

In this scenario, our study identified some radiological parameters that may assist the intervening interdisciplinary team in planning ultra-early management of patients with poor-grade aSAH..

Among the parameters found to be significantly correlated with 30-day mortality, the most interesting is the IVH ratio, which is the ratio of IVH volume to the total amount of IVH and ICH counterparts. In 2019, Panni et al. performed a detailed volumetric analysis of different bleeding distributions in poor-grade aSAH (5). These authors analyzed intracranial bleeding with its subarachnoid, intracerebral and intraventricular portions. They showed that: (1) global intracranial bleeding (sum of the three components) emerged as an independent predictor of good outcome (cutoff 24 mL); (2) relative percentage of ICH in global volume (10% of total) and pure SAH (64% of total) emerged as independent predictors of worse and better outcome, respectively; (3) global bleeding volume (cutoff 51 mL) along with global cerebral edema showed to independently predict 12-month mortality (5).

Several studies in the literature support the fact that IVH (25) and ICH (16, 18, 26) are negative and critical prognostic factors in aSAH. Compared to the subarachnoid counterpart, we found out that routine analysis of IVH and ICH fractions is a simple, fast and relatively easy-to-learn method for quantitative assessment of the hemorrhagic load on the initial CT scan. In particular we found that

an IVH ratio ≥ 40% is an independent predictor of mortality at 1 month after poor-grade aSAH.

These considerations can be implemented in the emergency scenario of poor-grade aSAH patients and, when combined with leading clinical and anamnestic information, can support the multidisciplinary neurovascular team in formulating clinical decisions and in a more informed discussion with the families during these delicate and eventful stages.

A further parameter that has been associated with mortality is the location of the aneurysm in the posterior circulation. The poor prognosis of ruptured intracranial aneurysms of the posterior circulation has been highlighted in previous studies (27, 28). In 2012 Inamasu et al. published a report (29) about acute cardiopulmonary dysfunction, particularly neurogenic pulmonary edema (NPE) and takotsubo-like cardiomyopathy (TLC) in poor-grade aSAH. They discovered that ruptured posterior circulation aneurysms were predictors of NPE and TLC (29) which may lead to an inauspicious outcome. Another reason may be related to the more frequent localization of dissecting aneurysms in the posterior circulation and their correlation with aneurysmal rebleeding that may lead to a fatal outcome (30, 31).

Finally, the presence of a spot sign on the initial CTA was found to be related to 1-month mortality. In 2017 Burkhardt et al. investigated the role of CTA spot signs in aSAH patients (32). In their multicenter study, patients with spot sign-positive aneurysmal ICH exhibited larger ICH volumes and a higher rate of intraprocedural aneurysm rupture; nevertheless, the long-term outcome was comparable to that of spot sign-negative ICH patients (32). As highlighted in that study (32), there are different theories about the pathophysiology of spot signs in aSAH. Some authors speculate that it is an indirect sign of vascular fragility affecting the small vessels around the ICH, including the aneurysm; other authors support the hypothesis that the dynamic of lightning-quick bleeding increases the possibility of "shear stress" damaging the surrounding ICH tissue and, as a consequence, the small vessels around the ICH (32).

Limitations

As far as limitations are concerned, the retrospective and single-center nature of the present study inevitably introduces selection and expertise biases that are naturally related to these study designs. Furthermore, we acknowledge that a time frame of 10 years, a relatively limited number of patients, the absence of long-term outcomes and the lack of data on functional outcomes, may decrease the strength of our findings.

Conclusion

The risk of death in poor-grade aSAH remains considerable despite maximal treatment. Notwithstanding the limitations of a retrospective study, our report points out some neuroradiological features that in the emergency setting, combined with leading clinical and anamnestic parameters, may support the multidisciplinary team in the difficult decision-making process and communication with family members from the earliest stages of poor-grade aSAH. Further prospective studies are warranted.

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 humans were approved by IRCCS Istituto delle Scienze Neurologiche di Bologna. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the next of kin in accordance with the requirements of the Ethics Board of IRCCS Istituto delle Scienze Neurologiche di Bologna.

Author contributions

AS: Data curation, Writing – original draft, Writing – review & editing. AR: Data curation, Writing – original draft, Writing – review & editing. ML: Data curation, Writing – review & editing. CZ: Data curation, Formal analysis, Methodology, Writing – review & editing. LB: Data curation, Formal analysis, Methodology, Writing – review & editing. MD: Writing – review & editing. CP: Writing – review & editing. ANC: Writing – review & editing. RA: Writing – review & editing. EM: Writing – review & editing. MM: Writing – review & editing. CS: Writing – review & editing. CC: Writing – review & editing. ALC: Writing – review & editing. CB: Writing – review & editing. LC: Writing – review & editing.

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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 taken as a potential conflict of interest.

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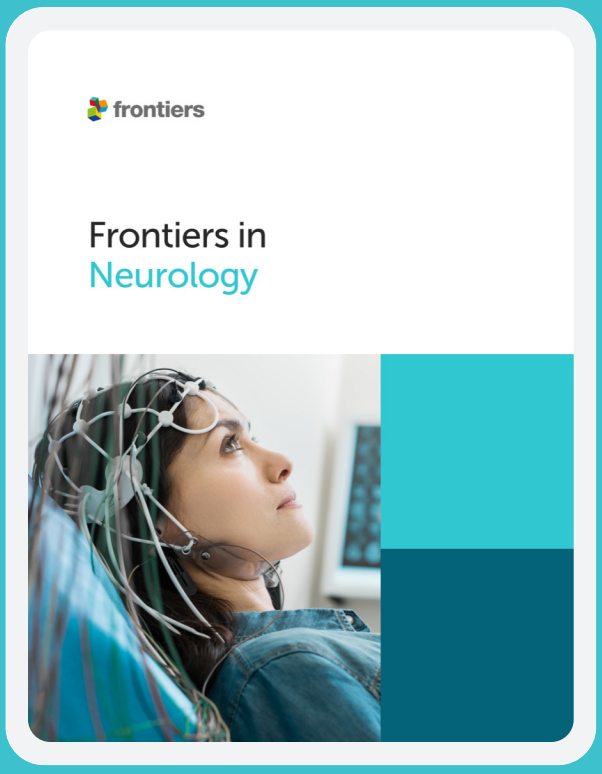

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