Effect of stress-induced hyperglycemia after non-traumatic non-aneurysmal subarachnoid hemorrhage on clinical complications and functional outcomes

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Abstract

Background

Despite having an overall benign course, non-traumatic non-aneurysmal subarachnoid hemorrhage (naSAH) is still accompanied by a risk of clinical complications and poor outcomes. Risk factors and mechanisms of complications and poor outcomes after naSAH remain unknown. Our aim was to explore the effect of stress-induced hyperglycemia (SIH) on complication rates and functional outcomes in naSAH patients.

Methods

We retrospectively reviewed patients with naSAH admitted to our institution between 2013 and 2018. SIH was identified according to previous criterion. Symptomatic vasospasm, delayed cerebral infarction, and hydrocephalus were identified as main complications. Outcomes were reviewed using a modified Rankin Scale (mRS) at discharge, 3 months, and 12 months. A statistical analysis of clinical, radiological, and laboratory risk factors of complications and outcomes was conducted.

Results

244 naSAH patients were incorporated in the cohort with 74 (30.3%) SIH. After adjusting for age, gender, hypertension, Hunt and Hess (HH) grade, modified Fisher Scale (mFS), intraventricular hemorrhage (IVH), and subarachnoid blood distribution, SIH was significantly associated with symptomatic vasospasm ($P < 0.001$, 12.176 [4.904–30.231]), delayed cerebral infarction ($P < 0.001$, 12.434 [3.850-40.161]), hydrocephalus ($P = 0.008$, 5.771 [1.570-21.222]), and poor outcome at 12 months ($P = 0.006$, 5.506 [1.632–18.581]), whereas the correlation between SIH and poor outcome at discharge ($P = 0.064$, 2.409 [0.951-6.100]) or 3 months ($P = 0.110$, 2.029 [0.852–4.833]) was not significant. Incorporation of SIH increased the area under curve (AUC) of ROC in the combined model for predicting symptomatic vasospasm ($P = 0.002$), delayed cerebral infarction ($P = 0.024$), hydrocephalus ($P = 0.037$), and 12-month poor outcome ($P = 0.087$).

Conclusions

SIH is a significant and independent risk factor for symptomatic vasospasm, delayed cerebral infarction, hydrocephalus, and long-term poor outcome in naSAH patients. Identifying SIH early after naSAH is important for decision-making and treatment planning.

Background

In approximately 15% of spontaneous subarachnoid hemorrhage (SAH) patients, the source of intracranial hemorrhage could not be determined [1–3]. These are termed non-traumatic non-aneurysmal SAH (naSAH) [4]. Compared with aneurysmal SAH (aSAH), naSAH has an overall benign course of disease [5]. However, some patients with naSAH still develop clinical complications or achieve poor functional outcomes despite their mild condition at admission [5–7]. The risk factors and pathophysiological mechanisms of clinical complications and poor outcomes after naSAH remain unknown.

Stress-induced hyperglycemia (SIH) is a transient hyperglycemia caused by an acute illness [8]. It is an adaptive immune-neurohormonal response to stress, and is often associated with increased morbidity and mortality [8]. Post-SAH hyperglycemia may cause secondary brain damage and cerebral vasospasm [9, 10]. Previous studies have shown that post-aSAH hyperglycemia was associated with a higher incidence of clinical complications and adverse outcomes, as well as higher mortality [11–14]. However, the prognostic value of SIH in patients with naSAH has not yet been established. Moreover, these studies did not differentiate between SIH and established diabetes mellitus (DM).

Therefore, the objective of this study was to examine the effect of SIH on naSAH patients' complication rates and functional outcomes, and to investigate the prognostic value of SIH for clinical complications and poor outcomes following naSAH.

Methods

Patients and management

We retrospectively reviewed patients suffering from naSAH that were admitted to our institution between January 1, 2013 and December 31, 2018. SAH was diagnosed by computed tomography (CT) or lumbar puncture. Non-traumatic SAH without confirmed bleeding source in cerebral digital subtraction angiography (DSA) examination within 72 hours of admission was identified as naSAH [15]. Additionally, patients that met the following criteria were excluded: (1) history of a head injury; (2) history of DM; (3) missing/lost radiological data; (4) missing/lost laboratory data. All aspects of this study were approved by the institutional board of the Second Affiliated Hospital of Zhejiang University School of Medicine. With their approval, patient consent was not required in this study.

All patients were treated according to SAH guidelines provided by the Neurocritical Care Society and the American Heart Association [16, 17]. Nimodipine was used to prevent cerebral vasospasm, and intravenous hydration was received to maintain euvolemia. Hemodynamic values were monitored via electrocardiogram at admission. All patients were not treated with insulin during hospitalization.

Data Collection

The baseline characteristics of the patients were reviewed, including age, gender, body mass index (BMI), as well as history of alcohol, smoking, and hypertension. The Hunt and Hess (HH) grade, modified Fisher Scale (mFS), and development of intraventricular hemorrhage (IVH) were used to assess SAH severity [18, 19]. Scores ranging from 3 to 5 for HH grade and 3 to 4 for mFS were considered high. According to the subarachnoid blood distribution, the patients were stratified into patients with perimesencephalic subarachnoid hemorrhage (PMH) and patients with non-PMH (NPMH) [4, 5, 15]. The laboratory data were investigated at admission, including serum glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), sodium, and potassium. SAH-related complications were reviewed during hospitalization, including symptomatic vasospasm, delayed cerebral infarction, rebleeding, hydrocephalus, and seizure [20]. We followed up with all patients in an outpatient clinic or by phone calls. The modified Rankin Scale (mRS) of patients at discharge, 3 months, and 12 months were investigated to assess the functional outcomes [21].

According to the latest consensus from the American Association of Clinical Endocrinologists and American Diabetes Association, SIH was defined as at least one of the following criteria: (1) an admission serum glucose level of 7.8 mmol/L (140 mg/dL) or more; (2) an in-hospital fasting serum glucose level of 7.0 mmol/L (126 mg/dL) or more on 2 or more determinations,; (3) a random serum glucose level of 11.1 mmol/L (200 mg/dL) or more without a prior history of DM [22].

Outcome Measurements

The primary outcomes included the development of clinical complications and poor outcomes. The main clinical complications included symptomatic vasospasm, delayed cerebral infarction, and hydrocephalus. Symptomatic vasospasm referred to either a focal neurological impairment or a decrease of at least 2 points on the Glasgow Coma Scale (GCS) lasting for at least 1 hour, which was not immediately apparent after SAH onset, and was not attributable to other causes [23]. Delayed cerebral infarction was diagnosed as a new infarction emerging on CT or magnetic resonance imaging (MRI), which had not originally been present within the first 24–48 hours after SAH onset, and was not attributable to other causes [23]. Hydrocephalus was defined as an expansion of the ventricular system on neuroimaging without obstructive cause or typical clinical presentation [24]. Functional outcomes were reviewed at discharge, 3 months, and 12 months using an mRS. Due to the overall favorable prognosis of naSAH patients, mRS scores ranging from 2 to 6 were considered poor outcome [15]. Two senior neurologists independently evaluated all clinical complications and functional outcomes of the patients. If there was a divergence, a third examiner would be used.

Statistical analysis

Statistical analysis was performed using IBM-SPSS V24.0 (SPSS Inc, Armonk, NY) with the statistical significance set at $P < 0.05$. Normally distributed variables were expressed as means ± standard deviations (SD), and non-normally distributed variables were expressed as median and interquartile range

(IQR). Categorical variables were expressed as the number of patients (percentage). Student's t-test and Mann-Whitney U-test were respectively used to compare the normally and non-normally distributed variables. Chi-square or Fisher's exact test was used to compare the categorical variables. Variables with a $P < 0.10$ in univariate analysis were included in the multivariate logistic regression model to identify the independent risk factors of clinical complications and poor outcomes. Odds ratio (OR) and 95% confidence interval (CI) were calculated. Receiver operating curve (ROC) was drawn using Prism 8 (GraphPad Software, Inc, LA Jolla, CA). The area under curve (AUC) was calculated to assess the ability of the models to predict clinical complications and poor outcomes.

Results

Patient characteristics

There were 296 patients diagnosed with naSAH in this study. Thirteen patients had a history of head injury. Twenty-two patients suffered from DM. Ten patients were missing radiological data and seven patients were missing laboratory data. Thus, 244 patients were included in the final cohort, with 74 (30.3%) suffering from SIH (Fig. 1). Among the patients, 108 (44.3%) were women, and the average age was 55.7 ± 11.2 years.

Table 1 shows the baseline characteristics, complications, and outcomes of the patients. Patients with SIH had a higher age ($P = 0.004$) and a higher proportion of hypertension ($P = 0.002$) and NPMH ($P = 0.010$). Regarding SAH severity, the HH grade 3–5 ($P < 0.001$), mFS 3–4 ($P = 0.003$), and IVH ($P = 0.026$) all correlated with SIH. In addition, SIH patients were more likely to develop SAH-related complications, including symptomatic vasospasm, delayed cerebral infarction, and hydrocephalus (all $P < 0.001$). They also had a higher proportion of mRS 2–6 at discharge ($P = 0.013$), 3 months ($P < 0.001$) and 12 months ($P < 0.001$). Figure 2 shows the subarachnoid blood distribution characteristic, HH grade, mFS, and IVH incidence of SIH and non-SIH patients. The main in-hospital complication rates and mRS distribution of the two groups of patients are shown in Fig. 3.

Table 1
Baseline characteristics, complications, and outcomes of SIH and non-SIH patients

	Total (n = 244)		
Variable	**SIH (n = 74)**	**non-SIH (n = 170)**	**P value**
Age, yr	58.8 ± 10.5	54.4 ± 11.2	0.004
Gender, female	39 (52.7)	69 (40.6)	0.080
Alcohol	27 (36.5)	67 (39.4)	0.666
Smoke	25 (33.8)	63 (37.1)	0.624
Hypertension	35 (47.3)	46 (27.1)	0.002
NPMH	33 (44.6)	47 (27.6)	0.010
HH grade 3–5	19 (25.7)	11 (6.5)	< 0.001
mFS 3–4	26 (35.1)	30 (17.6)	0.003
IVH	23 (31.1)	31 (18.2)	0.026
BMI, kg/m^2	23.9 ± 3.1	23.6 ± 2.7	0.474
Glucose, mmol/L	9.24 ± 2.03	6.35 ± 0.78	< 0.001
TC, mmol/L	4.86 ± 1.05	4.80 ± 1.05	0.732
TG, mmol/L	1.51 ± 0.88	1.39 ± 0.72	0.383
HDL-C, mmol/L	1.34 ± 0.34	1.28 ± 0.29	0.221
LDL-C, mmol/L	2.59 ± 0.81	2.68 ± 0.81	0.454
Sodium, mmol/L	139.3 ± 4.0	139.0 ± 3.3	0.491
Potassium, mmol/L	3.73 ± 0.47	3.81 ± 0.36	0.206
Symptomatic vasospasm	41 (55.4)	19 (11.2)	< 0.001
Delayed cerebral infarction	27 (36.5)	5 (2.9)	< 0.001
Rebleeding	3 (4.1)	3 (1.8)	0.541
Hydrocephalus	14 (18.9)	4 (2.4)	< 0.001
Seizure	0 (0)	3 (1.8)	0.555
mRS 2–6 at discharge	67 (90.5)	131 (77.1)	0.013

SIH: stress-induced hyperglycemia; NPMH: non-perimesencephalic subarachnoid hemorrhage; HH: Hunt and Hess; mFS: modified Fisher scale; IVH: intraventricular hemorrhage; BMI: body mass index; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; mRS: modified Rankin Scale

	Total (n = 244)		
mRS 2–6 at 3 months	19 (25.7)	15 (8.8)	< 0.001
mRS 2–6 at 12 months	14 (18.9)	5 (2.9)	< 0.001

SIH: stress-induced hyperglycemia; NPMH: non-perimesencephalic subarachnoid hemorrhage; HH: Hunt and Hess; mFS: modified Fisher scale; IVH: intraventricular hemorrhage; BMI: body mass index; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; mRS: modified Rankin Scale

Association Of Variables With Clinical Complications And Functional Outcomes

The associations between variables and clinical complications are shown in Table 2. The development of symptomatic vasospasm was significantly associated with NPMH, HH grade 3–5, mFS 3–4, IVH, higher admission serum glucose levels, and SIH (all $P < 0.001$). Patients with delayed cerebral infarction had higher age ($P = 0.028$) and admission serum glucose levels ($P < 0.001$), lower serum potassium levels ($P = 0.007$), and a higher proportion of hypertension, NPMH, HH grade 3–5, mFS 3–4, IVH, and SIH (all $P < 0.001$). The hydrocephalus group was significantly related to higher serum glucose levels at admission ($P = 0.001$) and a higher proportion of hypertension ($P = 0.002$), NPMH ($P < 0.001$), HH grade 3–5 ($P < 0.001$), mFS 3–4 ($P < 0.001$), IVH ($P = 0.003$), and SIH ($P < 0.001$).

Table 2
Association of variables with symptomatic vasospasm, delayed cerebral infarction, and hydrocephalus

	Symptomatic vasospasm			Delayed cerebral infarction			Hydrocephalus		
Variable	Yes (n = 60)	No (n = 184)	P value	Yes (n = 32)	No (n = 212)	P value	Yes (n = 18)	No (n = 226)	P value
Age, yr	58.0 ± 10.6	55.0 ± 11.3	0.068	59.8 ± 10.9	55.1 ± 11.1	0.028	59.1 ± 8.9	55.5 ± 11.3	0.191
Gender, female	26 (43.3)	82 (44.6)	0.868	16 (50.0)	92 (43.4)	0.483	7 (38.9)	101 (44.7)	0.633
Alcohol	19 (31.7)	75 (40.8)	0.209	11 (34.4)	83 (39.2)	0.605	6 (33.3)	88 (38.9)	0.638
Smoke	18 (30.0)	70 (38.0)	0.260	12 (37.5)	76 (35.8)	0.856	5 (27.8)	83 (36.7)	0.447
Hypertension	26 (43.3)	55 (29.9)	0.055	20 (62.5)	61 (28.8)	< 0.001	12 (66.7)	69 (30.5)	0.002
NPMH	42 (70.0)	38 (20.7)	< 0.001	24 (75.0)	56 (26.4)	< 0.001	15 (83.3)	65 (28.8)	< 0.001
HH grade 3–5	22 (36.7)	8 (4.3)	< 0.001	17 (53.1)	13 (6.1)	< 0.001	9 (50.0)	21 (9.3)	< 0.001
mFS 3–4	36 (60.0)	20 (10.9)	< 0.001	19 (59.4)	37 (17.5)	< 0.001	13 (72.2)	43 (19)	< 0.001
IVH	27 (45.0)	27 (14.7)	< 0.001	17 (53.1)	37 (17.5)	< 0.001	9 (50.0)	45 (19.9)	0.003
BMI, kg/m^2	23.9 ± 2.9	23.7 ± 2.8	0.613	23.4 ± 3.1	23.8 ± 2.8	0.415	23.0 ± 2.8	23.8 ± 2.8	0.232
Glucose, mmol/L	8.82 ± 2.42	6.70 ± 1.26	< 0.001	9.63 ± 2.72	6.86 ± 1.37	< 0.001	9.23 ± 2.35	7.06 ± 1.72	0.001
SIH	41 (68.3)	33 (17.9)	< 0.001	27 (84.4)	47 (22.2)	< 0.001	14 (77.8)	60 (26.5)	< 0.001
TC, mmol/L	4.76 ± 1.01	4.84 ± 1.06	0.667	4.87 ± 0.93	4.81 ± 1.06	0.793	5.02 ± 1.05	4.80 ± 1.05	0.434
TG, mmol/L	1.47 ± 0.73	1.41 ± 0.79	0.640	1.56 ± 0.74	1.41 ± 0.78	0.390	1.33 ± 0.49	1.44 ± 0.79	0.603

NPMH: non-perimesencephalic subarachnoid hemorrhage; HH: Hunt and Hess; mFS: modified Fisher scale; IVH: intraventricular hemorrhage; BMI: body mass index; SIH: stress-induced hyperglycemia; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol

	Symptomatic vasospasm			Delayed cerebral infarction			Hydrocephalus		
HDL-C, mmol/L	1.33 ± 0.35	1.28 ± 0.29	0.289	1.27 ± 0.39	1.30 ± 0.30	0.724	1.31 ± 0.29	1.29 ± 0.31	0.856
LDL-C, mmol/L	2.58 ± 0.82	2.68 ± 0.81	0.443	2.71 ± 0.82	2.65 ± 0.81	0.717	2.80 ± 0.79	2.64 ± 0.81	0.466
Sodium, mmol/L	139.4 ± 4.2	138.9 ± 3.3	0.358	139.1 ± 5.1	139.1 ± 3.3	0.995	138.5 ± 5.4	139.1 ± 3.4	0.479
Potassium, mmol/L	3.71 ± 0.44	3.81 ± 0.38	0.109	3.61 ± 0.50	3.81 ± 0.38	0.007	3.68 ± 0.48	3.79 ± 0.39	0.251

NPMH: non-perimesencephalic subarachnoid hemorrhage; HH: Hunt and Hess; mFS: modified Fisher scale; IVH: intraventricular hemorrhage; BMI: body mass index; SIH: stress-induced hyperglycemia; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol

Table 3 shows the associations between variables and functional outcomes. There were significant correlations between poor outcome at discharge and higher admission serum glucose levels (P = 0.048), SIH (P = 0.013), NPMH (P = 0.002), and higher SAH severity, including HH grade 3–5 (P = 0.038), mFS 3–4 (P = 0.002), and IVH (P = 0.002). Similar results were observed in 3-month and 12-month outcomes (all P < 0.05).

Table 3
Association of variables with functional outcomes at discharge, 3 months, and 12 months

	Poor outcome at discharge			Poor outcome at 3 months			Poor outcome at 12 months		
Variable	**Yes (n = 198)**	**No (n = 46)**	**P value**	**Yes (n = 34)**	**No (n = 210)**	**P value**	**Yes (n = 19)**	**No (n = 225)**	**P value**
Age, yr	56.2 ± 10.8	53.8 ± 12.5	0.188	57.6 ± 11.6	55.4 ± 11.1	0.283	59.1 ± 11.1	55.5 ± 11.1	0.171
Gender, female	85 (42.9)	23 (50.0)	0.384	14 (41.2)	94 (44.8)	0.696	4 (21.1)	104 (46.2)	0.060
Alcohol	77 (38.9)	17 (37.0)	0.808	10 (29.4)	84 (40.0)	0.239	7 (36.8)	87 (38.7)	0.875
Smoke	72 (36.4)	16 (34.8)	0.841	13 (38.2)	75 (35.7)	0.776	9 (47.4)	79 (35.1)	0.285
Hypertension	65 (32.8)	16 (34.8)	0.800	16 (47.1)	65 (31.0)	0.064	10 (52.6)	71 (31.6)	0.061
NPMH	74 (37.4)	6 (13.0)	0.002	22 (64.7)	58 (27.6)	< 0.001	15 (78.9)	65 (28.9)	< 0.001
HH grade 3–5	29 (14.6)	1 (2.2)	0.038	15 (44.1)	15 (7.1)	< 0.001	10 (52.6)	20 (8.9)	< 0.001
mFS 3–4	54 (27.3)	2 (4.3)	0.002	17 (50.0)	39 (18.6)	< 0.001	12 (63.2)	44 (19.6)	< 0.001
IVH	52 (26.3)	2 (4.3)	0.002	13 (38.2)	41 (19.5)	0.015	9 (47.4)	45 (20.0)	0.006
BMI, kg/m^2	23.8 ± 2.8	23.4 ± 2.6	0.380	24.3 ± 3.2	23.6 ± 2.7	0.230	23.9 ± 3.6	23.7 ± 2.7	0.843
Glucose, mmol/L	7.34 ± 1.94	6.74 ± 1.38	0.048	8.78 ± 3.14	6.97 ± 1.41	0.002	9.56 ± 2.89	7.03 ± 1.60	0.001
SIH	67 (33.8)	7 (15.2)	0.013	19 (55.9)	55 (26.2)	< 0.001	14 (73.7)	60 (26.7)	< 0.001
TC, mmol/L	4.82 ± 1.07	4.81 ± 0.93	0.942	4.75 ± 0.83	4.83 ± 1.08	0.721	4.79 ± 0.91	4.82 ± 1.06	0.904
TG, mmol/L	1.42 ± 0.72	1.47 ± 0.96	0.684	1.44 ± 0.70	1.43 ± 0.78	0.926	1.41 ± 0.69	1.43 ± 0.78	0.919
HDL-C, mmol/L	1.31 ± 0.30	1.23 ± 0.32	0.159	1.36 ± 0.36	1.28 ± 0.30	0.242	1.38 ± 0.38	1.29 ± 0.30	0.212

NPMH: non-perimesencephalic subarachnoid hemorrhage; HH: Hunt and Hess; mFS: modified Fisher scale; IVH: intraventricular hemorrhage; BMI: body mass index; SIH: stress-induced hyperglycemia; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol

	Poor outcome at discharge			Poor outcome at 3 months			Poor outcome at 12 months		
LDL-C, mmol/L	2.65 ± 0.85	2.67 ± 0.63	0.865	2.60 ± 0.75	2.67 ± 0.82	0.691	2.60 ± 0.86	2.66 ± 0.81	0.753
Sodium, mmol/L	139.1 ± 3.7	138.9 ± 3.1	0.752	139.0 ± 4.8	139.1 ± 3.3	0.885	138.7 ± 5.3	139.1 ± 3.4	0.674
Potassium, mmol/L	3.79 ± 0.39	3.74 ± 0.46	0.419	3.68 ± 0.50	3.80 ± 0.38	0.195	3.71 ± 0.52	3.79 ± 0.39	0.410

NPMH: non-perimesencephalic subarachnoid hemorrhage; HH: Hunt and Hess; mFS: modified Fisher scale; IVH: intraventricular hemorrhage; BMI: body mass index; SIH: stress-induced hyperglycemia; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol

Effect of Sih On Clinical Complications And Functional Outcomes

SIH was found to be significantly associated with clinical complications and adverse outcomes in our cohort. Therefore, we evaluated the effect of SIH on clinical complications and functional outcomes in multivariate logistic regression analysis. As is depicted in Fig. 4, when accompanied by SIH, there was a 12.176 (P < 0.001, 95% CI 4.904–30.231) increase in the odds of developing symptomatic vasospasm, a 12.434 (P < 0.001, 95% CI 3.850-40.161) increase in the odds of developing delayed cerebral infarction, and a 5.771 (P = 0.008, 95% CI 1.570-21.222) increase in the odds of developing hydrocephalus after adjustment for covariates, including age, gender, hypertension, HH grade, mFS, IVH, and subarachnoid blood distribution characteristic. Regarding functional outcomes, there were no significant associations between SIH and poor outcome at discharge (P = 0.064, OR 2.409, 95% CI 0.951-6.100) or at 3 months (P = 0.110, OR 2.029, 95% CI 0.852–4.833) after adjusting for the above covariates. Interestingly, SIH was significantly and independently associated with poor outcome at 12 months (P = 0.006, OR 5.506, 95% CI 1.632–18.581).

Prognostic value of SIH for clinical complications and functional outcomes

The combined models were constructed to predict clinical complications and functional outcomes. The results are displayed in Table 4. Model 1 was obtained by incorporating variables with a P value < 0.10 in univariate analysis and using a forward stepwise method of multivariate logistic regression analysis. SIH was incorporated in the prediction of symptomatic vasospasm (P < 0.001, OR 11.507, 95% CI 4.807–27.544), delayed cerebral infarction (P < 0.001, OR 13.874, 95% CI 4.424–43.507), hydrocephalus (P = 0.003, OR 6.474, 95% CI 1.915–21.894), discharge poor outcome (P = 0.038, OR 2.512, 95% CI 1.051–6.001), 3-month poor outcome (P = 0.006, OR 2.980, 95% CI 1.376–6.452), and 12-month poor outcome (P = 0.010, OR 4.556, 95% CI 1.447–14.345). Model 2 was obtained in the same manner, but with exclusion of the variable SIH.

Table 4
Multivariate logistic regression models for predicting clinical complications and functional outcomes

	Model 1 (SIH included)		Model 2 (SIH excluded)	
Variable	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Symptomatic vasospasm				
SIH	11.507 (4.807–27.544)	< 0.001	N/A	N/A
NPMH	3.096 (1.079–8.884)	0.036	2.724 (1.086–6.830)	0.033
HH grade 3–5	3.417 (1.002–11.658)	0.050	4.908 (1.744–13.812)	0.003
mFS 3–4	5.007 (1.661–15.091)	0.004	4.047 (1.550-10.566)	0.004
IVH	2.636 (1.045–6.650)	0.040	2.510 (1.119–5.629)	0.026
Delayed cerebral infarction				
SIH	13.874 (4.424–43.507)	< 0.001	N/A	N/A
Hypertension	3.200 (1.149–8.912)	0.026	4.109 (1.632–10.346)	0.003
NPMH	5.447 (1.878–15.796)	0.002	5.330 (2.035–13.963)	0.001
HH grade 3–5	7.457 (2.373–23.430)	0.001	9.760 (3.578–26.624)	N/A
Hydrocephalus				
SIH	6.474 (1.915–21.894)	0.003	N/A	N/A
Hypertension	3.822 (1.221–11.970)	0.021	4.491 (1.522–13.252)	0.007
mFS 3–4	9.389 (2.944–29.940)	< 0.001	10.967 (3.612–33.292)	< 0.001
Poor outcome at discharge				

Model 1 was obtained by incorporating variables with a P value < 0.10 in univariate analysis and using a forward stepwise method of multivariate logistic regression analysis. Model 2 was obtained in the same manner, but excluding the variable SIH.

SIH: stress-induced hyperglycemia; OR: odds ratio; CI: confidence interval; NPMH: non-perimesencephalic subarachnoid hemorrhage; HH: Hunt and Hess; mFS: modified Fisher scale; IVH: intraventricular hemorrhage; N/A: not applicable

	Model 1 (SIH included)		Model 2 (SIH excluded)	
SIH	2.512 (1.051–6.001)	0.038	N/A	N/A
mFS 3–4	N/A	N/A	6.436 (1.487–27.852)	0.013
IVH	7.092 (1.650-30.478)	0.008	6.024 (1.389–26.127)	0.016
Poor outcome at 3 months				
SIH	2.980 (1.376–6.452)	0.006	N/A	N/A
NPMH	4.195 (1.918–9.173)	< 0.001	2.990 (1.296–6.899)	0.010
HH grade 3–5	N/A	N/A	6.806 (2.739–16.911)	< 0.001
Poor outcome at 12 months				
SIH	4.556 (1.447–14.345)	0.010	N/A	N/A
NPMH	5.086 (1.483–17.445)	0.010	5.580 (1.665–18.706)	0.005
HH grade 3–5	4.144 (1.322–12.988)	0.015	6.234 (2.116–18.366)	0.001
Model 1 was obtained by incorporating variables with a P value < 0.10 in univariate analysis and using a forward stepwise method of multivariate logistic regression analysis. Model 2 was obtained in the same manner, but excluding the variable SIH.				
SIH: stress-induced hyperglycemia; OR: odds ratio; CI: confidence interval; NPMH: non-perimesencephalic subarachnoid hemorrhage; HH: Hunt and Hess; mFS: modified Fisher scale; IVH: intraventricular hemorrhage; N/A: not applicable				

ROC analysis was performed to evaluate the predictive ability of the models (Fig. 5). In the ROC analysis, model 1 had a significantly higher AUC compared with model 2 for the prediction of symptomatic vasospasm (0.893 [0.848–0.929] vs. 0.828 [0.774–0.873]; P = 0.002). Similar results were observed when predicting delayed cerebral infarction (0.931 [0.892–0.959] vs. 0.871 [0.823–0.911]; P = 0.024) and hydrocephalus (0.890 [0.843–0.926] vs. 0.810 [0.755–0.857]; P = 0.037). However, in the prediction of poor outcomes at discharge (0.662 [0.599–0.721] vs. 0.671 [0.609–0.730]; P = 0.775) and 3 months (0.736 [0.676–0.790] vs. 0.747 [0.687-0.800]; P = 0.659), the AUC of model 1 was not higher than that of model 2. It is worth noting that, although not statistically significant, the AUC of model 1 was higher than that of model 2 in predicting 12-month poor outcome (0.854 [0.804–0.896] vs. 0.814 [0.759–0.861]; P = 0.087). Thus, incorporation of SIH increased the ability of the model for the prediction of symptomatic vasospasm, delayed cerebral infarction, hydrocephalus, and 12-month poor outcome.

Discussion

To our knowledge, this is the first study to explore the association of SIH with complication rates and functional outcomes in naSAH. This study found that SIH after naSAH was significantly and independently associated with the development of symptomatic vasospasm, delayed cerebral infarction, hydrocephalus, and a poor outcome at 12 months after adjusting for demographic data, hypertension history, subarachnoid blood distribution characteristic, and SAH severity. Taking SIH into consideration with risk factors improved the prediction of symptomatic vasospasm, delayed cerebral infarction, hydrocephalus, and 12-month poor outcome after naSAH, although it had limited benefits in the prediction of poor outcomes at discharge or at 3 months. These findings highlight the importance of considering SIH in the decision-making algorithm and treatment planning following naSAH.

SIH is a transient hyperglycemia after acute illness or injury caused by the activation of stress-neuroendocrine axis [8]. Previous research suggested that post-stroke SIH may be a biomarker of stroke severity [25, 26]. One meta-analysis involving 16 studies showed that 69% (range, 29 to 100%) of patients suffered a SIH after aSAH [13]. The proportion of SIH in our study cohort (30.3%) was much lower than this proportion, reflecting the low severity of naSAH. In one study, SIH occurred in 32.0% of naSAH patients, which was similar to the proportion in our cohort [27]. An early study confirmed a significant correlation between high serum glucose levels and high clinical severity assessed by HH grade in aSAH patients ($P = 0.001$) [26]. In addition, Santucci et al. reported that SIH after aSAH was significantly associated with radiologically estimated intracranial blood volume ($P < 0.001$) [28]. Our results in naSAH cohort were consistent with these findings. In our study, patients with SIH had higher HH grade ($P = 0.001$), mFS ($P = 0.003$) and a higher proportion of IVH ($P = 0.026$; Fig. 2). Additionally, in the characteristic of subarachnoid blood distribution, the proportion of NPMH in SIH patients was higher than that of non-SIH patients ($P = 0.010$), which may be due to the fact that NPMH was more similar to aSAH a higher severity [4, 5]. These results may indicate the systemic stress response caused by severe brain injury after SAH.

Several studies have explored the relationship between hyperglycemia and complication rates and adverse outcomes after aSAH. Badjatia et al. found that mean serum glucose levels during hospitalization correlated with the development of symptomatic vasospasm after aSAH ($P < 0.001$) [11]. Juvela and colleagues reported that hyperglycemia following aSAH were related to delayed cerebral infarction and hydrocephalus [12]. A meta-analysis incorporated 8 studies for the analysis of the association between hyperglycemia and clinical outcome after aSAH and found that post-aSAH hyperglycemia was associated with an increased risk of poor clinical outcome at 3 or 6 months [13]. These results supported our findings. However, these studies only identified patients with hyperglycemia, but did not differentiate between SIH patients and DM patients. Since pre-existing hyperglycemia before SAH onset could not reflect the activation of stress response caused by SAH, our study excluded patients with a history of DM. Moreover, these studies only described the association of hyperglycemia after SAH with functional outcomes within 6 months, but did not explore its relationship with long-term outcomes. Our study identified patients with SIH based on the latest consensus from the American Association of

Clinical Endocrinologists and American Diabetes Association, and demonstrated the independent association of SIH with symptomatic vasospasm ($P < 0.001$), delayed cerebral infarction ($P < 0.001$) and hydrocephalus ($P = 0.008$) in the naSAH cohort. After adjusting for demographic data, hypertension history, subarachnoid blood distribution characteristic, and SAH severity, SIH was significantly associated with adverse outcomes at 12 months ($P = 0.006$), although no significant correlation was found between SIH and poor outcomes at discharge ($P = 0.064$) or at 3 months ($P = 0.110$; Fig. 4).

The deleterious effects of activation of stress-neuroendocrine axis after SAH may explain the correlation between SIH and adverse outcomes. The stress response can induce the activation of hypothalamus-pituitary-adrenal axis and sympathetic autonomic nervous system, as well as induce the secretion of glucagon, catecholamines, and corticosteroids [8]. The metabolic disorders caused by these factors may lead to inflammation, systemic damage, and various complications [8]. Sympathetic activation and serum catecholamine elevation after aSAH has been confirmed in previous studies, and were found to be related to symptomatic vasospasm and unfavorable outcomes [29, 30]. It was found that inhibition of sympathetic activity by beta-blockers could reduce cerebral vasospasm rates and improve functional outcomes after aSAH [31, 32]. In an animal study, inhibition of central sympathetic nerve activation through renal denervation significantly prevented cerebral vasospasm after SAH [33]. In addition, hyperglycemia may aggravate early brain injury (EBI) after SAH. Currently, new insight suggests that EBI within 72 hours after SAH onset may lay the foundation for subsequent pathophysiological changes and poor outcomes of patients. The pathological mechanisms of EBI include oxidative stress, platelet activation, inflammation, and neuronal apoptosis [34–37]. One animal experiment found that hyperglycemia could increase reactive oxygen species (ROS) production through activating protein kinase C after stroke, thereby exacerbating oxidative stress [38]. In another study, hyperglycemia aggravated neuronal apoptosis through the activation of extrinsic caspase cascade via extracellular regulated kinase (ERK) signal pathway after experimental SAH [9]. In addition, hyperglycemia was also found to be related to the activation of platelets and the increase of pro-inflammatory cytokines [39].

In the present study, SIH was a significant and independent risk factor of symptomatic vasospasm, delayed cerebral infarction, hydrocephalus, and 12-month poor outcome in patients with naSAH. Taking SIH into consideration with risk factors improved the prediction of symptomatic vasospasm, delayed cerebral infarction, hydrocephalus, and 12-month poor outcome. Biomarkers for predicting complications and poor outcomes after naSAH have not yet been established. Currently, prediction of unfavorable outcomes after naSAH primarily still depends on the severity of SAH, which is assessed using HH grade, mFS, and occurrence of IVH. However, naSAH patients often have minor SAH severity at admission [5–7]. Thus, SAH severity has limited value in predicting poor outcomes in this population. Since the identification of SIH could easily be performed in any institution, it should be an important reference for predicting complications and poor outcomes of naSAH patients. In addition, this study suggested that the stress response and resulting hyperglycemia after naSAH may be harmful to patients. Therefore, we recommend proper glycemic management for naSAH patients with SIH.

This study had several limitations. First, we did not detect the patients' serum endocrine hormones, such as cortisol and catecholamines, to better explore the activation of the stress-neuroendocrine axis after naSAH. Second, we lost the data regarding glycated hemoglobin (HbA1c) of the patients to define SIH more precisely through relative hyperglycemia. To address this problem, we defined SIH through the serum glucose levels at admission and during hospitalization according to the latest consensus from the American Association of Clinical Endocrinologists and American Diabetes Association. The proportion of naSAH patients in our cohort who developed SIH (30.3%) was comparable to a previous study that defined SIH by relative hyperglycemia (32.0%) [27]. Third, our study did not reveal whether interventions on hyperglycemia after naSAH could assist in reducing risk of the development of complications and poor outcomes. Finally, our study was a single-center retrospective study. Further multi-center prospective studies are needed to verify our findings.

Conclusions

This study found that SIH was a significant and independent risk factor for symptomatic vasospasm, delayed cerebral infarction, hydrocephalus, and long-term poor outcomes in patients with naSAH. SIH was useful for predicting complications and long-term prognosis of naSAH, although its benefit in the prediction of short-term prognosis was limited. In addition, this study may allude to the underlying mechanism of stress-neuroendocrine axis in the pathogenesis of naSAH. Our findings highlight the importance of identifying SIH early after naSAH for decision-making and treatment planning.

Abbreviations

SAH
subarachnoid hemorrhage
naSAH
non-aneurysmal subarachnoid hemorrhage
aSAH
aneurysmal subarachnoid hemorrhage
SIH
stress-induced hyperglycemia
DM
diabetes mellitus
CT
computed tomography
DSA
digital subtraction angiography
BMI
body mass index
HH

Hunt and Hess
mFS
modified Fisher Scale
IVH
intraventricular hemorrhage
PMH
perimesencephalic subarachnoid hemorrhage
NPMH
non-perimesencephalic subarachnoid hemorrhage
TC
total cholesterol
TG
triglyceride
HDL-C
high-density lipoprotein cholesterol
LDL-C
low-density lipoprotein cholesterol
mRS
modified Rankin Scale
GCS
Glasgow Coma Scale
MRI
magnetic resonance imaging
SD
standard deviation
IQR
interquartile range
OR
odds ratio
CI
confidence interval
ROC
receiver operating curve
AUC
area under curve
EBI
early brain injury
ROS
reactive oxygen species
ERK

extracellular regulated kinase
HbA1c
glycated hemoglobin.

Declarations

Ethics approval and consent to participate

This study was approved by Institutional board of the Second Hospital affiliated to Zhejiang University.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZYZ wrote the manuscript; YZ and SC designed the study; AKZ and XYW collected the study data; YJF, SC, and CL revised the manuscript; YBL, HSX, and YJL participated in the design and coordination of the study. All authors read and approved the final version of the manuscript.

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References

1. Schuss P, Hadjiathanasiou A, Brandecker S, Wispel C, Borger V, Guresir A, Vatter H, Guresir E. Risk factors for shunt dependency in patients suffering from spontaneous, non-aneurysmal subarachnoid hemorrhage. Neurosurgical review. 2019;42(1):139–45.
2. Lin N, Zenonos G, Kim AH, Nalbach SV, Du R, Frerichs KU, Friedlander RM, Gormley WB. Angiogram-negative subarachnoid hemorrhage: relationship between bleeding pattern and clinical outcome. Neurocritical care. 2012;16(3):389–98.
3. Boswell S, Thorell W, Gogela S, Lyden E, Surdell D. Angiogram-negative subarachnoid hemorrhage: outcomes data and review of the literature. Journal of stroke cerebrovascular diseases: the official journal of National Stroke Association. 2013;22(6):750–7.
4. Konczalla J, Platz J, Schuss P, Vatter H, Seifert V, Guresir E. Non-aneurysmal non-traumatic subarachnoid hemorrhage: patient characteristics, clinical outcome and prognostic factors based on a single-center experience in 125 patients. BMC Neurol. 2014;14:140.
5. Al-Mufti F, Merkler AE, Boehme AK, Dancour E, May T, Schmidt JM, Park S, Connolly ES, Lavine SD, Meyers PM, et al. Functional Outcomes and Delayed Cerebral Ischemia Following Nonperimesencephalic Angiogram-Negative Subarachnoid Hemorrhage Similar to Aneurysmal Subarachnoid Hemorrhage. Neurosurgery. 2018;82(3):359–64.
6. Konczalla J, Kashefiolasl S, Brawanski N, Lescher S, Senft C, Platz J, Seifert V. Cerebral vasospasm and delayed cerebral infarctions in 225 patients with non-aneurysmal subarachnoid hemorrhage: the underestimated risk of Fisher 3 blood distribution. Journal of neurointerventional surgery. 2016;8(12):1247–52.
7. Gupta SK, Gupta R, Khosla VK, Mohindra S, Chhabra R, Khandelwal N, Gupta V, Mukherjee KK, Tewari MK, Pathak A, et al. Nonaneurysmal nonperimesencephalic subarachnoid hemorrhage: is it a benign entity? Surgical neurology. 2009;71(5):566–71. discussion 571,571 – 562,572.
8. Mifsud S, Schembri EL, Gruppetta M. Stress-induced hyperglycaemia. Br J Hosp Med. 2018;79(11):634–9.
9. Huang YH, Chung CL, Tsai HP, Tzou RD, Wu SC, Chai CY, Lee TC, Kwan AL. Impact of hyperglycemia on neuronal apoptosis after subarachnoid hemorrhage in rodent brain: An experimental research. International journal of surgery. 2020;83:246–52.
10. Huang YH, Chung CL, Tsai HP, Wu SC, Chang CZ, Chai CY, Lee TC, Kwan AL. Hyperglycemia Aggravates Cerebral Vasospasm after Subarachnoid Hemorrhage in a Rat Model. Neurosurgery. 2017;80(5):809–15.
11. Badjatia N, Topcuoglu MA, Buonanno FS, Smith EE, Nogueira RG, Rordorf GA, Carter BS, Ogilvy CS, Singhal AB. Relationship between hyperglycemia and symptomatic vasospasm after subarachnoid hemorrhage. Critical care medicine. 2005;33(7):1603–9. quiz 1623.
12. Juvela S, Siironen J, Kuhmonen J. Hyperglycemia, excess weight, and history of hypertension as risk factors for poor outcome and cerebral infarction after aneurysmal subarachnoid hemorrhage.

Journal of neurosurgery. 2005;102(6):998–1003.

13. Kruyt ND, Biessels GJ, de Haan RJ, Vermeulen M, Rinkel GJ, Coert B, Roos YB. Hyperglycemia and clinical outcome in aneurysmal subarachnoid hemorrhage: a meta-analysis. Stroke. 2009;40(6):e424–30.
14. Bian L, Liu L, Wang C, Hussain M, Yuan Y, Liu G, Wang W, Zhao X: **Hyperglycemia within day 14 of aneurysmal subarachnoid hemorrhage predicts 1-year mortality**. *Clinical neurology and neurosurgery* 2013, **115**(7):959–964.
15. Fang Y, Shao A, Wang X, Lu J, Wu H, Ren R, Huang Y, Lenahan C, Xu J, Chen S, et al. Deep venous drainage variant rate and degree may be higher in patients with perimesencephalic than in non-perimesencephalic angiogram-negative subarachnoid hemorrhage. European radiology. 2021;31(3):1290–9.
16. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, Hoh BL, Kirkness CJ, Naidech AM, Ogilvy CS, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke. 2012;43(6):1711–37.
17. Diringer MN, Bleck TP, Claude Hemphill J 3rd, Menon D, Shutter L, Vespa P, Bruder N, Connolly ES Jr, Citerio G, Gress D, et al: **Critical care management of patients following aneurysmal subarachnoid hemorrhage**: **recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference**. *Neurocritical care* 2011, **15**(2):211–240.
18. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES Jr, MacDonald RL, Mayer SA. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery. 2006;59(1):21–7. discussion 21–27.
19. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. Journal of neurosurgery. 1968;28(1):14–20.
20. Macdonald RL, Schweizer TA. Spontaneous subarachnoid haemorrhage. Lancet. 2017;389(10069):655–66.
21. Pace A, Mitchell S, Casselden E, Zolnourian A, Glazier J, Foulkes L, Bulters D, Galea I. A subarachnoid haemorrhage-specific outcome tool. Brain. 2018;141(4):1111–21.
22. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, Inzucchi SE, Ismail-Beigi F, Kirkman MS, Umpierrez GE, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Endocrine practice: official journal of the American College of Endocrinology the American Association of Clinical Endocrinologists. 2009;15(4):353–69.
23. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, Mendelow AD, Juvela S, Yonas H, Terbrugge KG, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. Stroke. 2010;41(10):2391–5.

24. Fang Y, Shao Y, Lu J, Dong X, Zhao X, Zhang J, Chen S. The effectiveness of lumbar cerebrospinal fluid drainage in aneurysmal subarachnoid hemorrhage with different bleeding amounts. Neurosurgical review. 2020;43(2):739–47.
25. Tziomalos K, Dimitriou P, Bouziana SD, Spanou M, Kostaki S, Angelopoulou SM, Papadopoulou M, Giampatzis V, Savopoulos C, Hatzitolios AI. Stress hyperglycemia and acute ischemic stroke in-hospital outcome. Metab Clin Exp. 2017;67:99–105.
26. Alberti O, Becker R, Benes L, Wallenfang T, Bertalanffy H. Initial hyperglycemia as an indicator of severity of the ictus in poor-grade patients with spontaneous subarachnoid hemorrhage. Clinical neurology neurosurgery. 2000;102(2):78–83.
27. Ray B, Ludwig A, Yearout LK, Thompson DM, Bohnstedt BN. Stress-Induced Hyperglycemia After Spontaneous Subarachnoid Hemorrhage and Its Role in Predicting Cerebrospinal Fluid Diversion. World neurosurgery. 2017;100:208–15.
28. Santucci JA, Ross SR, Greenert JC, Aghaei F, Ford L, Hollabaugh KM, Cornwell BO, Wu DH, Zheng B, Bohnstedt BN, et al: **Radiological Estimation of Intracranial Blood Volume and Occurrence of Hydrocephalus Determines Stress-Induced Hyperglycemia After Aneurysmal Subarachnoid Hemorrhage**. *Translational stroke research* 2018.
29. Ogura T, Satoh A, Ooigawa H, Sugiyama T, Takeda R, Fushihara G, Yoshikawa S, Okada D, Suzuki H, Araki R, et al. Characteristics and prognostic value of acute catecholamine surge in patients with aneurysmal subarachnoid hemorrhage. Neurological research. 2012;34(5):484–90.
30. Benedict CR, Loach AB. Clinical significance of plasma adrenaline and noradrenaline concentrations in patients with subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry. 1978;41(2):113–7.
31. Chalouhi N, Daou B, Okabe T, Starke RM, Dalyai R, Bovenzi CD, Anderson EC, Barros G, Reese A, Jabbour P, et al. Beta-blocker therapy and impact on outcome after aneurysmal subarachnoid hemorrhage: a cohort study. Journal of neurosurgery. 2016;125(3):730–6.
32. Neil-Dwyer G, Walter P, Cruickshank JM. Beta-blockade benefits patients following a subarachnoid haemorrhage. Eur J Clin Pharmacol. 1985;28 **Suppl**:25–9.
33. Takemoto Y, Hasegawa Y, Hayashi K, Cao C, Hamasaki T, Kawano T, Mukasa A, Kim-Mitsuyama S. The Stabilization of Central Sympathetic Nerve Activation by Renal Denervation Prevents Cerebral Vasospasm after Subarachnoid Hemorrhage in Rats. Translational stroke research. 2020;11(3):528–40.
34. Chen S, Feng H, Sherchan P, Klebe D, Zhao G, Sun X, Zhang J, Tang J, Zhang JH. Controversies and evolving new mechanisms in subarachnoid hemorrhage. Progress in neurobiology. 2014;115:64–91.
35. Wang X, Li S, Ma J, Wang C, Chen A, Xin Z, Zhang J. Effect of Gastrodin on Early Brain Injury and Neurological Outcome After Subarachnoid Hemorrhage in Rats. Neurosci Bull. 2019;35(3):461–70.
36. Luo X, Li L, Xu W, Cheng Y, Xie Z. HLY78 Attenuates Neuronal Apoptosis via the LRP6/GSK3beta/beta-Catenin Signaling Pathway After Subarachnoid Hemorrhage in Rats. Neurosci Bull. 2020;36(10):1171–81.

37. Fumoto T, Naraoka M, Katagai T, Li Y, Shimamura N, Ohkuma H. The Role of Oxidative Stress in Microvascular Disturbances after Experimental Subarachnoid Hemorrhage. Translational stroke research. 2019;10(6):684–94.
38. Anderson RE, Tan WK, Martin HS, Meyer FB. Effects of glucose and PaO2 modulation on cortical intracellular acidosis, NADH redox state, and infarction in the ischemic penumbra. Stroke. 1999;30(1):160–70.
39. Kruyt ND, Biessels GJ, DeVries JH, Luitse MJ, Vermeulen M, Rinkel GJ, Vandertop WP, Roos YB. Hyperglycemia in aneurysmal subarachnoid hemorrhage: a potentially modifiable risk factor for poor outcome. Journal of cerebral blood flow metabolism: official journal of the International Society of Cerebral Blood Flow Metabolism. 2010;30(9):1577–87.

Figures

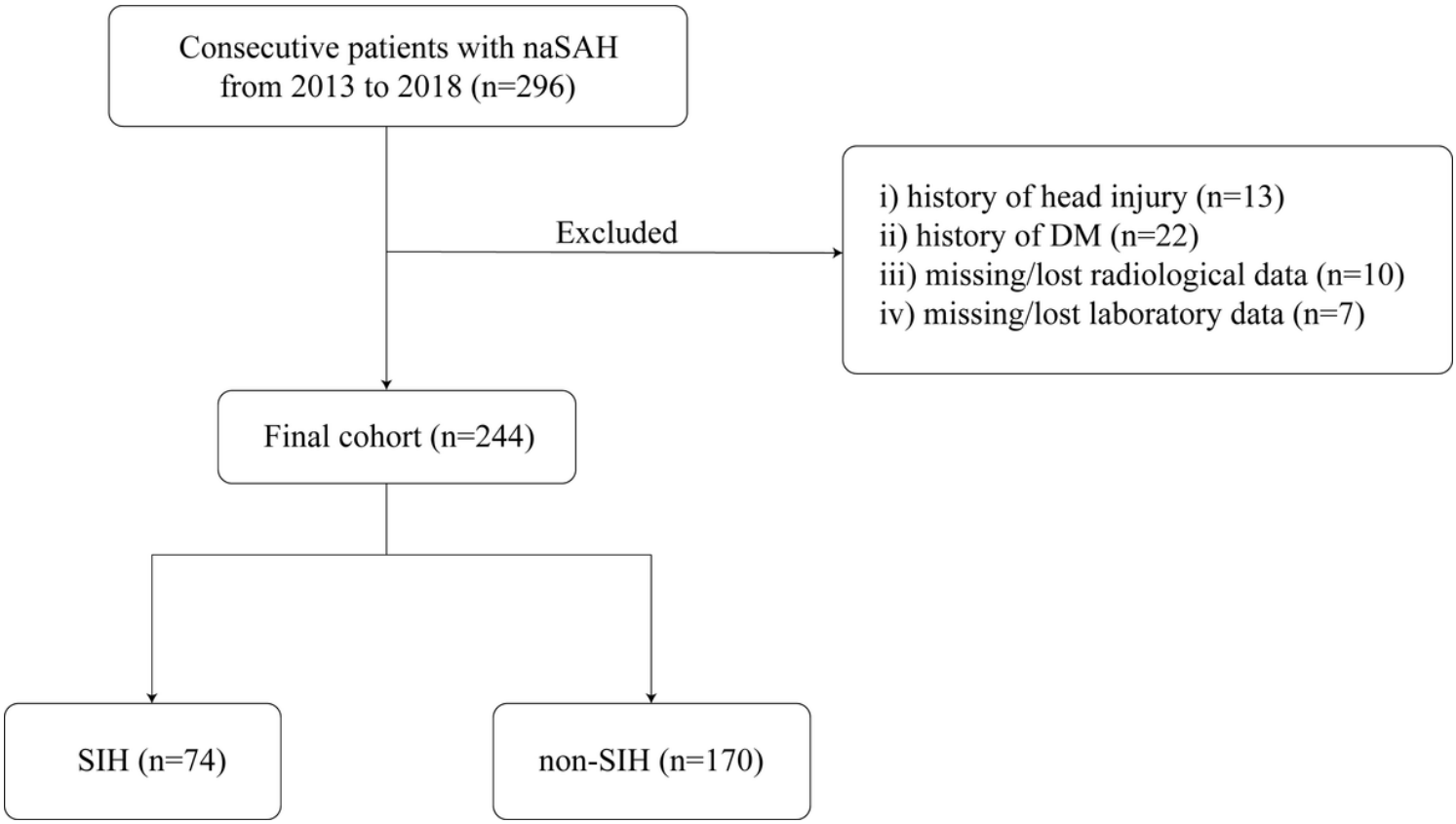

Figure 1

Flowchart of the studied patients A total of 296 naSAH patients were reviewed. After selection, 244 patients were included with 74 SIH and 170 non-SIH. naSAH: non-aneurysmal subarachnoid hemorrhage; DM: diabetes mellitus; SIH: stress-induced hyperglycemia

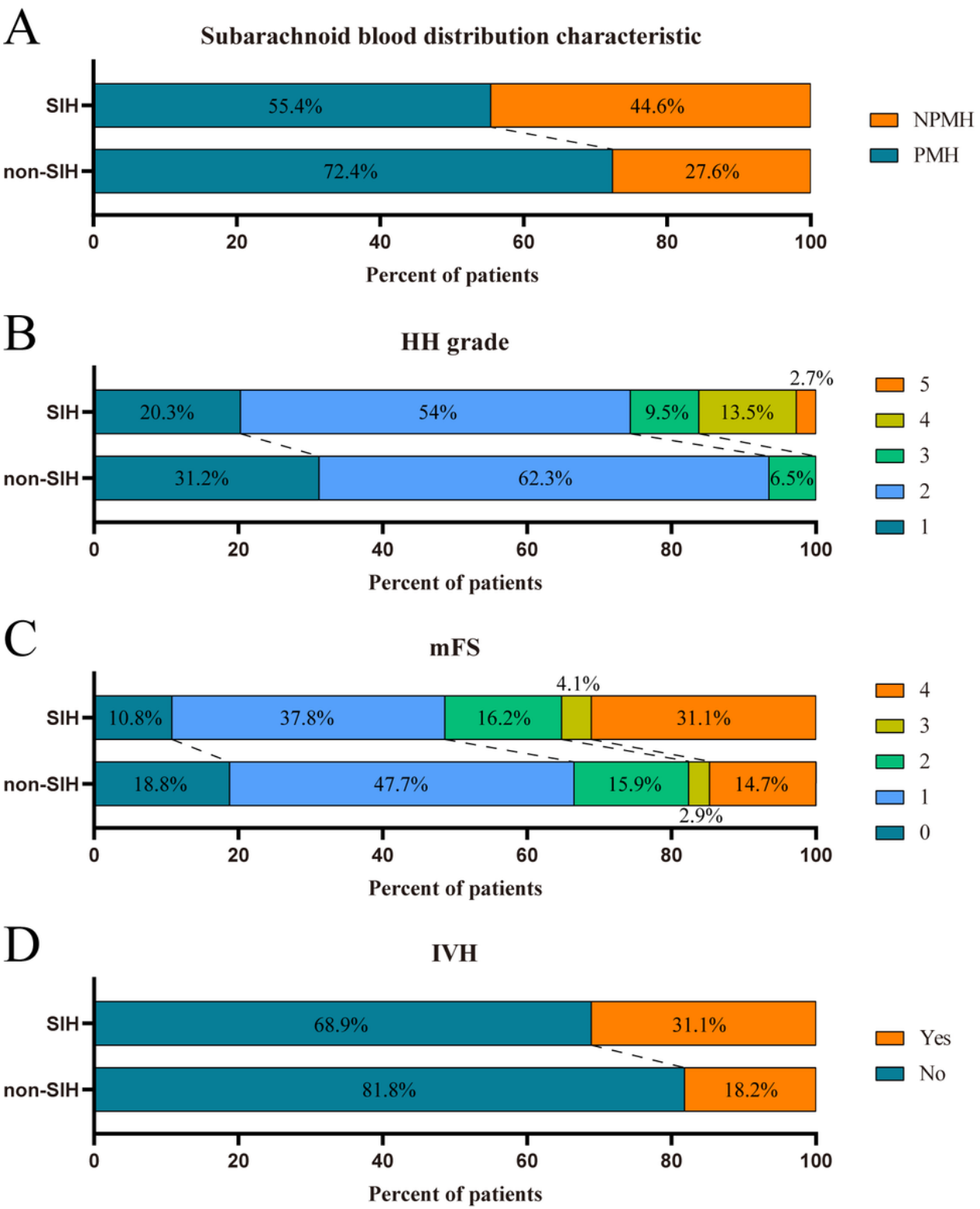

Figure 2

Subarachnoid blood distribution characteristic, HH grade, mFS, and IVH incidence in SIH and non-SIH patients Compared with non-SIH patients, patients with SIH had a higher proportion of NPMH (A, P = 0.010), higher HH grade (B, P = 0.001), higher mFS (C, P = 0.003), and a higher proportion of IVH (D, P = 0.026). SIH: stress-induced hyperglycemia; NPMH: non-perimesencephalic subarachnoid hemorrhage;

PMH: perimesencephalic subarachnoid hemorrhage; HH: Hunt and Hess; mFS: modified Fisher scale; IVH: intraventricular hemorrhage

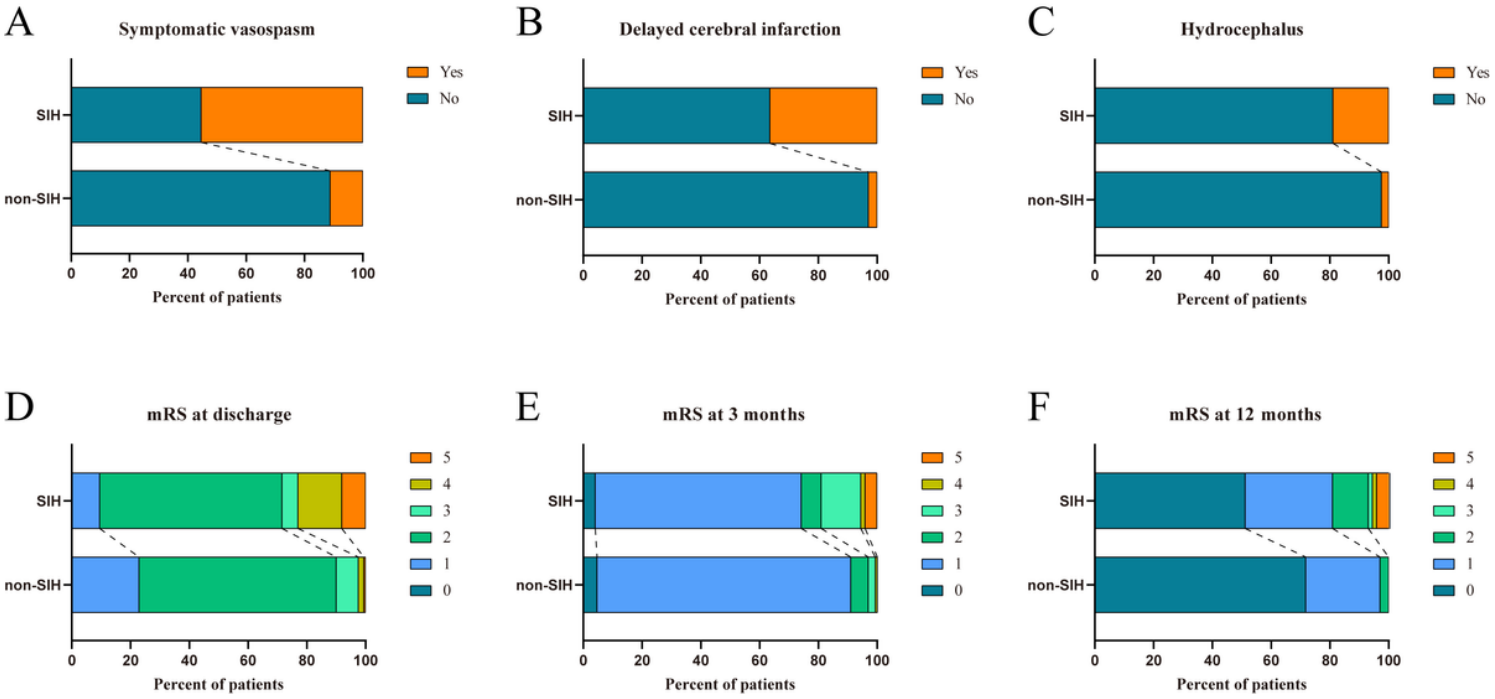

Figure 3

Incidence of symptomatic vasospasm, delayed cerebral infarction, and hydrocephalus, as well as distribution of mRS in SIH and non-SIH patients Compared with non-SIH patients, SIH patients were more likely to develop symptomatic vasospasm (A, $P < 0.001$), delayed cerebral infarction (B, $P < 0.001$), and hydrocephalus (C, $P < 0.001$). They also had higher mRS at discharge (D, $P < 0.001$), 3 months (E, $P = 0.001$), and 12 months (F, $P < 0.001$). mRS: modified Rankin Scale; SIH: stress-induced hyperglycemia

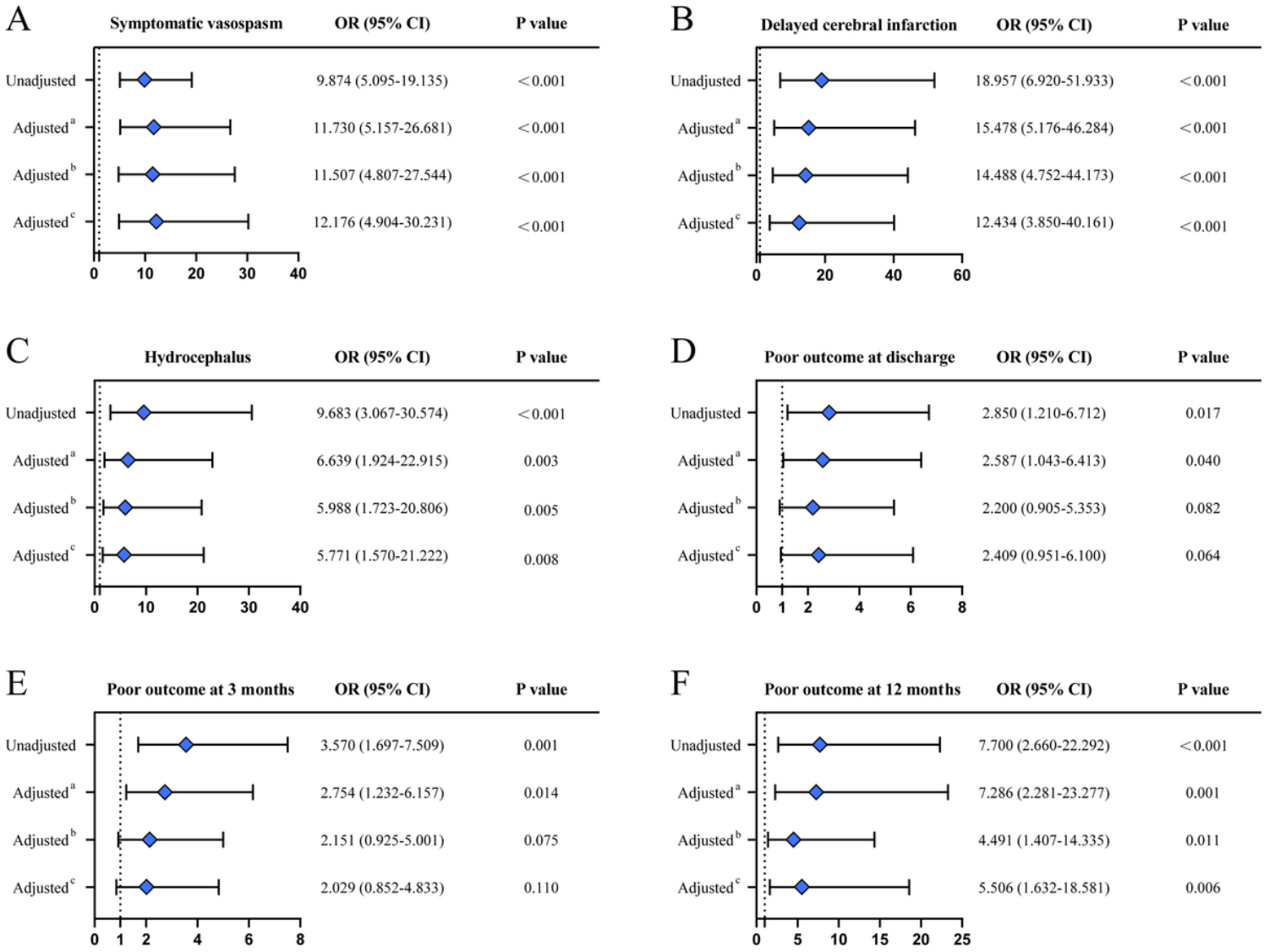

Figure 4

Unadjusted and adjusted OR for SIH to evaluate the effect of SIH on clinical complications and functional outcomes After adjusting for age, gender, hypertension, HH grade, mFS, IVH, and subarachnoid blood distribution characteristic, SIH was still significantly associated with symptomatic vasospasm (A, P < 0.001), delayed cerebral infarction (B, P < 0.001), hydrocephalus (C, P = 0.008), and 12-month poor outcome (F, P = 0.006), but was not significantly associated with discharge poor outcome (D, P = 0.064) and 3-month poor outcome (E, P = 0.110). aAdjusted for age, gender, hypertension, and subarachnoid blood distribution characteristic. bAdjusted for HH grade, mFS, IVH, and subarachnoid blood distribution characteristic. cAdjusted for age, gender, hypertension, HH grade, mFS, IVH, and subarachnoid blood distribution characteristic. OR: odds ratio; SIH: stress-induced hyperglycemia; HH: Hunt and Hess; mFS: modified Fisher scale; IVH: intraventricular hemorrhage

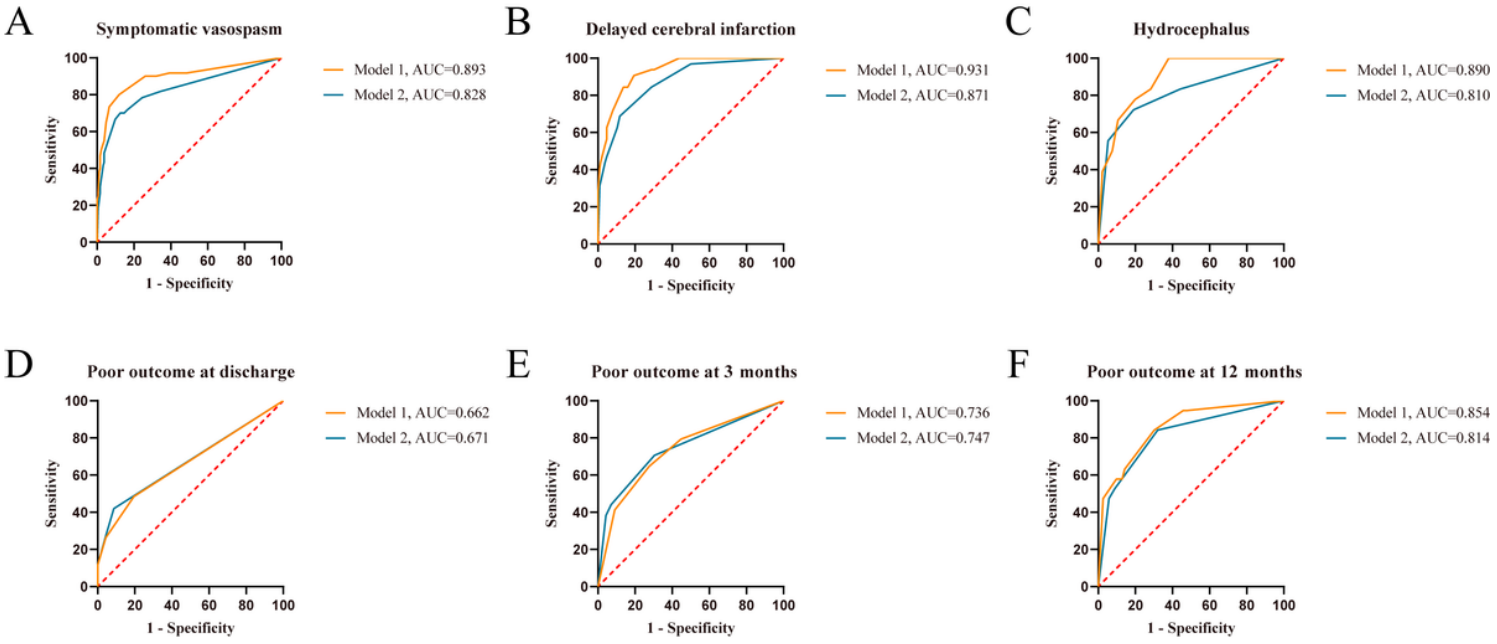

Figure 5

ROC curve for combined model to predict clinical complications and functional outcomes. In predicting symptomatic vasospasm (A, P = 0.002), delayed cerebral infarction (B, P = 0.024), and hydrocephalus (C, P = 0.037), model 1 had a significantly higher AUC than model 2. In predicting discharge poor outcome (D, P = 0.775) and 3-month poor outcome (E, P = 0.659), the AUC of model 1 was not higher than that of model 2. In the prediction of 12-month poor outcome (F, P = 0.087), the AUC of model 1 was higher than that of model 2, although it was not statistically significant. ROC: receiver operating curve; AUC: area under curve