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Original Article

NIHSS: A Possible Predictor of Outcomes in Patients with Aneurysmal Subarachnoid Hemorrhage

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Abstract:

Background: The National Institutes of Health Stroke Scale (NIHSS) is a powerful and commonly used tool for predicting the prognosis of patients with either ischemic stroke or intracerebral hemorrhage. In this study, we investigated whether a correlation exists between the NIHSS score and the prognosis in aSAH patients and examined the predictive ability.

Methods: This retrospective analysis included two cohorts of patients undergoing endovascular coiling for aSAH. Logistic regression models were used to predict the functional outcomes, which were evaluated using a modified Rankin Scale (mRS) at 3 months. Decision curve analysis (DCA) and a calibration curve were employed to assess the predictive accuracy and reliability of the models.

Results: In the derivation cohort, the NIHSS on admission (OR, 1.08; 95% CI, 1.04–1.13, $P < 0.001$) was an independent predictor of the 3-month mRS in aSAH patients. The area under the curve (AUC) for the NIHSS was 0.806 with a 95% CI (0.771, 0.841). By incorporating the NIHSS into the fundamental model, which included age, modified Fisher scale score, and leukocyte count, a significant improvement in discrimination for unfavorable outcomes was observed (ACU 0.784 vs. 0.845). In the two validation groups, adding the NIHSS on admission (OR, 1.08; 95% CI, 1.04–1.11 and OR, 1.2; 95% CI, 1.04–1.38) to the fundamental model resulted in a similar increase in overall performance.

Conclusions: The higher NIHSS score on admission showed the worse prognosis in patients treated with endovascular embolization for aSAH.

Key words: Aneurysmal subarachnoid hemorrhage; NHISS; Prediction; Outcome

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is associated with higher morbidity and mortality rates compared to either ischemic stroke or intracerebral hemorrhage[1]. The estimated mortality rate for aSAH is 30%, and a significant proportion of surviving patients remain functionally dependent[2]. Only 25% of aSAH patients recover to their pre-illness state without requiring assistance from family members for activities of daily living[3]. Therefore, it is crucial to acquire an early identification tool for patients with aSAH suffering from a high risk of poor prognosis in order to choose optimal treatments and make prudent decisions regarding their care[4].

The most commonly used tools for assessing disease severity and predicting patient outcomes in subarachnoid hemorrhage (SAH) are the Hunt–Hess (HH) Scale and the modified Fisher scale (mFS)[5-11]. However, HH scores cannot identify the minor neurological deficits of aSAH. Studies have illustrated that the HH scale is limited by its subjectivity and vague language, which may reduce its accuracy[12,13]. Meanwhile, the mFS also shows insufficient accuracy, and it requires a CT scan, making it less convenient[14].

The National Institutes of Health Stroke Scale (NIHSS) is the most commonly used tool for the comprehensive evaluation of neurological deficits in patients with ischemic stroke[15]. Several studies have suggested that the NIHSS score upon admission can be utilized to predict the prognosis of patients with intracerebral hemorrhage, as it is associated with both functional outcomes and mortality[16,17.] However, further investigation is required to determine whether such an association is an independent predictor and if it is applicable to patients with aSAH[18,19]. Therefore, we conducted a retrospective analysis to examine the potential predicting ability and accuracy of the NIHSS on admission using aSAH patients with a 3-month modified Rankin Scale (mRS) prognosis.

Patient Data

This retrospective analysis included two cohorts. The model derivation cohort included consecutive adult patients treated with endovascular coil embolization for spontaneous aSAH admitted to the First Affiliated Hospital of Shantou University Medical College between January 2014 and September 2021. External validation was conducted using an independent cohort consisting of consecutive adult patients treated with endovascular coil embolization for spontaneous aSAH from two other centers, Sun Yat-sen University Affiliated Jieyang People's Hospital (December 2019 to May 2021) and the Affiliated Shantou Hospital of Sun Yat-sen University (January 2019 to December 2022). This study was conducted in accordance with the Declaration of Helsinki (reviewed in Brazil in 2013). The protocol was approved by the Institutional Review Board (IRB). Informed consent was waived by the committee and by the IRB.

Spontaneous aSAH was confirmed by CT scan, and intracranial aneurysm was confirmed by either computed tomography angiography or digital subtraction angiography for inclusion in the final analysis. Typically, aneurysm treatment is performed within 24 hours of hospital admission using endovascular coiling. Acute hydrocephalus is treated by inserting an external ventricular drain to measure the intracranial pressure (ICP)[20]. Elevated ICP (> 20 mmHg) is managed conservatively through cerebrospinal fluid drainage, head elevation, osmotic therapy, deep sedation, and relaxation. Patients whose ICP increases despite conservative management are referred for decompressive craniectomy. Cerebral perfusion pressure is maintained above 60 mmHg. Post-hemorrhagic hydrocephalus is treated with ventriculoperitoneal shunt. A follow-up CT scan of the head is performed within 24 hours after aneurysm treatment if there are clinical indications (such as weakness, increased ICP, or clinical deterioration). All aSAH patients received standard nursing care according to the guidelines of the American Stroke Association[21].

Data Extraction

Variables collected upon admission included patient characteristics such as age, sex, blood pressure, comorbidity (e.g., hypertension and diabetes), clinical scores (modify Fisher scale score, Hunt–Hess grade, Glasgow Coma Scale (GCS) score, NIHSS score),[17] which were documented by three doctors (Y.Z., Z.D., and J.C.) who were blinded to other clinical data when scoring. Laboratory findings, including serum white blood cell count, neutrophil count, monocyte count, lymphocyte count, serum calcium level, and blood glucose level, were also recorded.

Definition of Follow-Up and Outcome

The modified Rankin Scale (mRS) score was used to assess patients at 3-month follow-up. A mRS score of 3–6 is defined as an adverse outcome. Follow-up assessments for all patients were conducted by two trained healthcare personnel either at the clinic, hospital, or through telephone interviews. Patient data were also entered into the follow-up system available to the clinical physicians.[22]

Statistical Analysis

Statistical analyses were conducted using Statistical Product and Service Solutions (26th version; IBM Corporation, Armonk, New York, USA) and R (version 4.3.2; R Foundation, Vienna, Austria)[23–26]. Categorical variables were analyzed using chi-square or Fisher's exact test, and continuous variables were analyzed using Student's t-test or Kruskal–Wallis test.

Univariate and multivariate logistic regression analyses were conducted to determine the correlation between baseline NIHSS score and the 3-month mRS outcome. All parameters showing a statistical trend ($p < 0.1$) in univariate analysis with a retaining statistical trend ($p < 0.1$) in multivariate analysis were analyzed using the forward selection procedure to identify independent factors that were relevant to unfavorable outcomes at 3 months. The results were presented as odds ratios (OR) with 95% confidence intervals (CI). These independent risk factors were separated into two models: one based on established independent risk factors (such as age, modified Fisher grade, WBC), and the other included these plus the NIHSS score. The area under the receiver operating characteristic (ROC) curve (AUC) was used to examine the predictive value of the models. Net reclassification improvement and integrated discrimination improvement were conducted to compare the predictive power of two models. Finally, calibration curve and decision curve analysis (DCA) were conducted to evaluate the clinical value of the models[27,28].

Results

Characteristics of the Derivation Cohort

The patient selection process is illustrated in Figure 1. After excluding ineligible records, a total of 1,195 patients were included in the study, with 690 in the training cohort and 505 in the validation cohort. Table 1 shows the baseline characteristics of the derivation patients. The majority of the patients (61.4%) were female, and the median age was 57.1 years (interquartile range: 45.9–68.3). Among the patients with aSAH, 265 (38.4%) achieved unfavorable outcomes, with mRS scores of 4–6 at 3 months. Patients with poor outcomes were older and had higher NIHSS, GCS, mFS, and HH scores upon admission, as well as higher levels of leukocytes, neutrophils, and monocytes, compared to patients with good outcomes (mRS scores of 0–3) ($p < 0.05$).

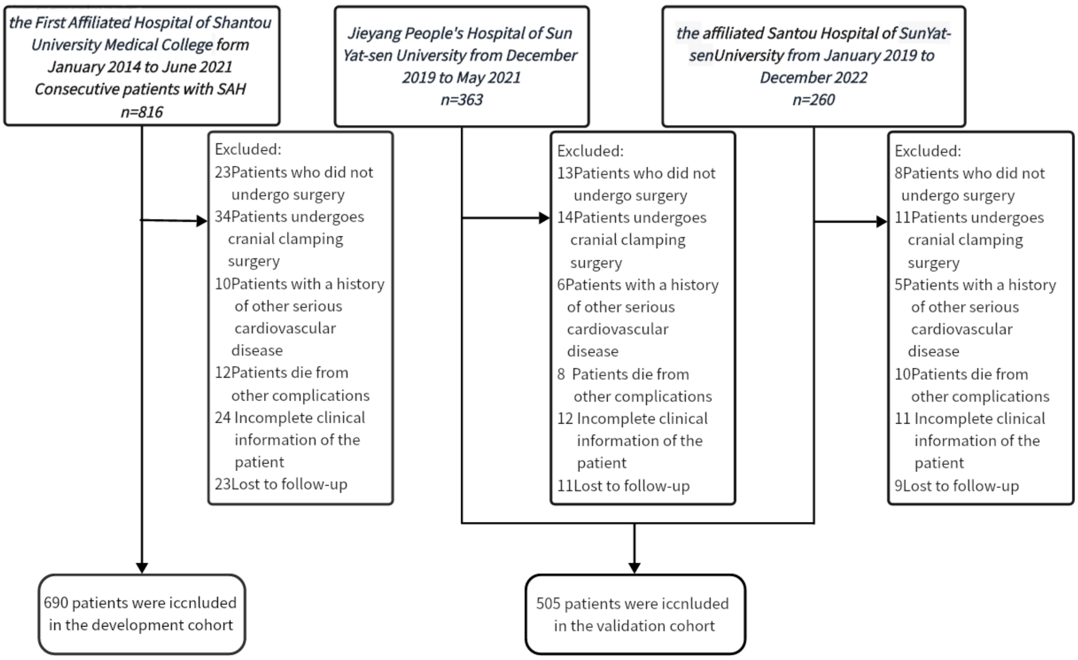

Figure 1 Flowchart depicting the inclusion of 690 and 505 patients into the development cohort and the validation cohort, respectively.

Table 1: Differences between with favorable prognosis group and the unfavorable prognosis group in the derivation cohort (univariate analysis)

Variables	Total	Favorable	Unfavorable	*P*-value

	(n = 690)	prognosis (n = 425)	prognosis (n = 265)	
Gender (male, n%)	266 (38.6)	163 (38.4)	103 (38.9)	0.892
Age (year, mean±SD)	57.1 ± 11.2	55.5 ± 10.7	59.5 ± 11.5	**< 0.001**
Hypertension, n%	270(39.1)	153 (36)	117 (44.2)	0.033
mFS grade, n%				**< 0.001**
0	2 (0.3)	0 (0)	2 (0.8)	
1	107 (15.6)	91 (21.4)	16 (6.1)	
2	349 (50.7)	238 (56)	111 (42.2)	
3	138 (20.1)	48 (11.3)	90 (34.2)	
4	92 (13.4)	48 (11.3)	44 (16.7)	
Hunt-Hess grade, n%				**< 0.001**
1	132 (19.1)	106 (25.3)	26 (9.6)	
2	131 (19.2)	110 (26.3)	21 (8)	
3	266 (39.1)	175 (41.8)	91 (34.7)	
4	129 (18.9)	27 (6.4)	102 (38.9)	
5	23 (3.4)	1 (0.2)	22 (8.4)	
Level on GCS score, n%				**< 0.001**
Severe (3–8 score)	113 (16.4)	14 (3.3)	99 (37.4)	
Moderate (9–12 score)	91 (13.2)	39 (9.2)	52 (19.6)	
Mild (13–15 score)	486 (70.4)	372 (87.5)	114 (43)	
NIHSS score	9.6 ± 13.5	3.7 ± 7.6	19.1 ± 15.4	**< 0.001**
SAP, mmHg	157.8 ± 27.2	155.0 ± 24.8	162.3 ± 30.1	**< 0.001**
DAP, mmHg	93.1 ± 17.1	92.3 ± 15.7	94.3 ± 19.1	0.145
Blood glucose, mmol/L	9.2 ± 3.1	8.3 ± 2.4	10.6 ± 3.6	**< 0.001**
Serum calcium level, mmol/L	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.2	0.670
Leukocyte count, 10^9/L	14.4 ± 5.2	13.0 ± 4.5	16.7 ± 5.4	**< 0.001**
Neutrophil count, 10^9/L	12.0 ± 5.0	10.7 ± 4.4	13.9 ± 5.2	**< 0.001**
Lymphocyte count, 10^9/L	1.7 ± 1.2	1.6 ± 1.1	1.8 ± 1.4	0.011
Platelet count, 10^9/L	239.9 ± 65.0	236.3 ± 64.4	245.8 ± 65.7	0.059
Monocyte count, 10^9/L	0.6 ± 0.4	0.6 ± 0.3	0.7 ± 0.4	**< 0.001**

NIHSS as a Predictor of Poor Outcomes

In the univariate regression analysis, several factors, including sex, age, admission GCS score, mFS score, NIHSS score, HH grade, leukocyte count, neutrophil count, monocyte count, and systolic blood pressure, showed significant associations with poor patient prognoses ($p < 0.1$). The multivariate logistic regression analysis, which incorporated these factors, showed that higher NIHSS scores were significantly associated with poor patient prognoses ($p < 0.001$, odds ratio [OR] = 1.08, 95% confidence interval [CI] = 1.04–1.13). Older age ($p < 0.001$, OR = 1.04, 95% CI = 1.02–1.06), higher mFS scores ($p = 0.019$, OR = 1.31, 95% CI = 1.04–1.64), and higher leukocyte counts (p = 0.002, OR = 1.09, 95% CI = 1.03–1.15) were also independently associated with poor patient outcomes (Table 2).

In the ROC curve analysis, the AUC for the NIHSS score was 0.806 (95% CI: 0.771–0.841). The sensitivity, specificity, positive predictive value, and negative predictive value of the NIHSS score were 65.28%, 84.47%, 72.38%, and 79.6%, respectively. Comparing the ROC curves of the other prognostic predictors, the NIHSS score had the highest AUC, at 0.806 (0.771, 0.841), followed by the mFS, at 0.657 (0.619, 0.696), HH grade, at 0.754 (0.717, 0.791), and GCS, at 0.783 (0.747, 0.819) (all $P < 0.001$), indicating that the NIHSS score had the highest predictive value among the clinical scales evaluated (Figure 2).

Table2: Multivariate regression analysis of factors associated with unfavorable outcome (mRS of 3-6) at 3 mounths.

Variable	OR (95% CI)	P- Value
Age	1.04 (1.02, 1.06)	<0.001
mFS grade		
0, I, II	1	1
III, IV	1.31 (1.04, 1.64)	0.019
NIHSS score	1.08 (1.04, 1.13)	<0.001
Neutrophil count	1.09 (1.03, 1.14)	0.002

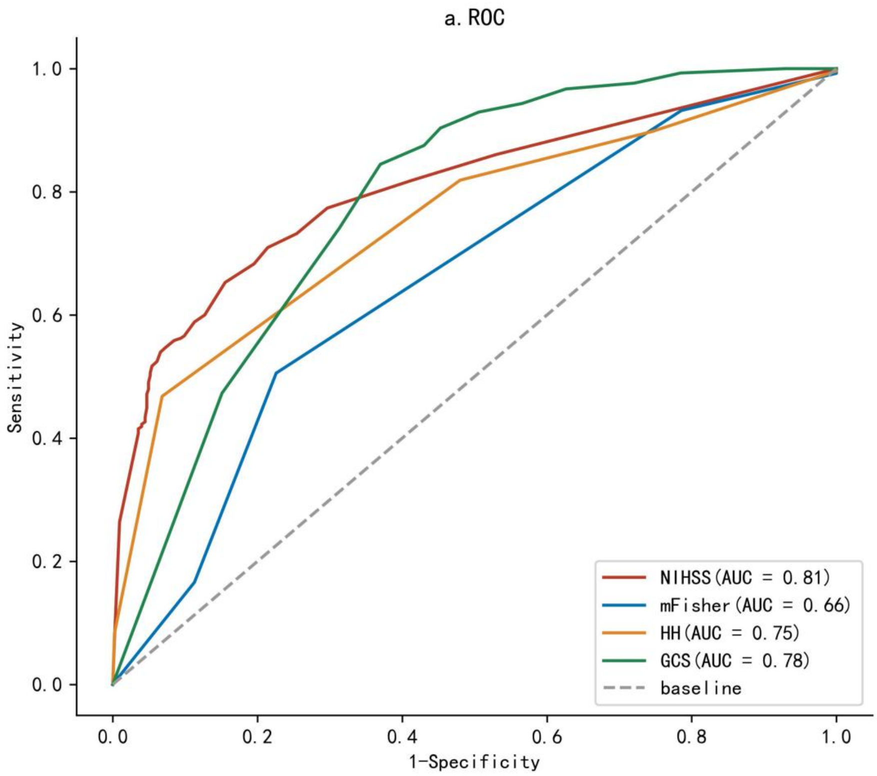

Figure 2 The receiver operating curve (ROC) for the NIHSS, Glasgow Coma Scale, Hunt–Hess grade, and modified Fisher grade.

Predictive Value of Models for Poor Outcomes

The predictive performance of the two models (i.e., with or without NIHSS) in the training cohort is shown in Figure 3. Compared with the basic model, which is based on conventional factors (age, modified Fisher grade, and WBC), adding the NIHSS to the modeling (full model) significantly improved the overall performance of the model (ACU 0.784 [0.749, 0.820] vs. 0.845 [0.814, 0.875]; $P < 0.001$). The DCA curves also demonstrated the higher predictive ability of the full model (Figure 4A). In addition, the calibration curves showed better agreement between predictions and observations in the full model compared to in the basic model (Figure 4B).

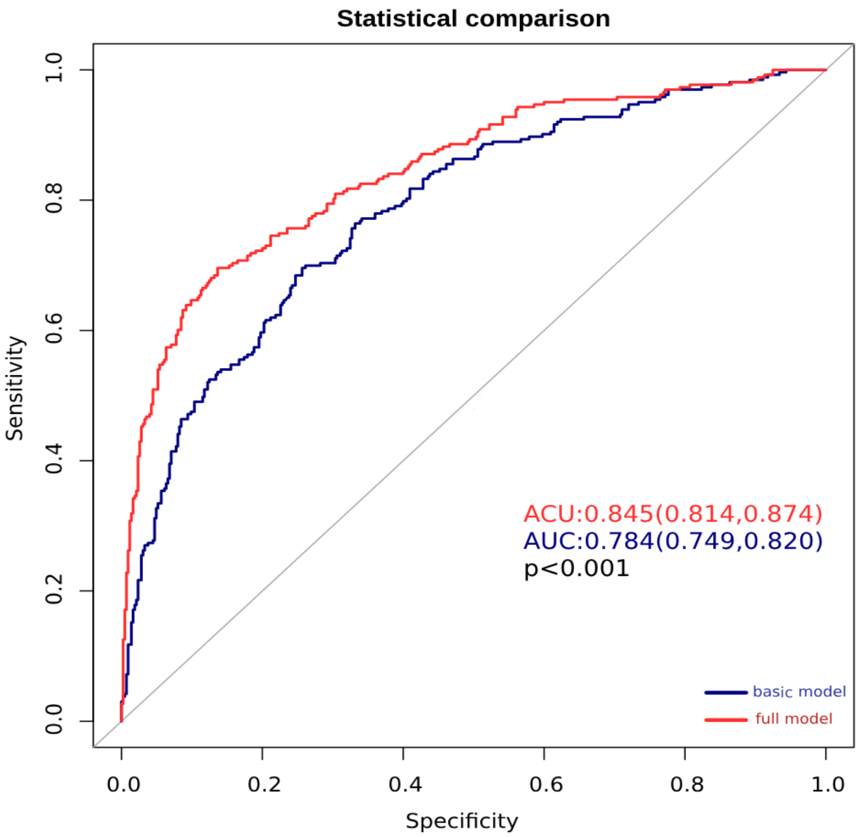

Figure 3 The basic model included the age, modified Fisher grade, and leukocyte count. The full model included the basic model plus the NIHSS score.

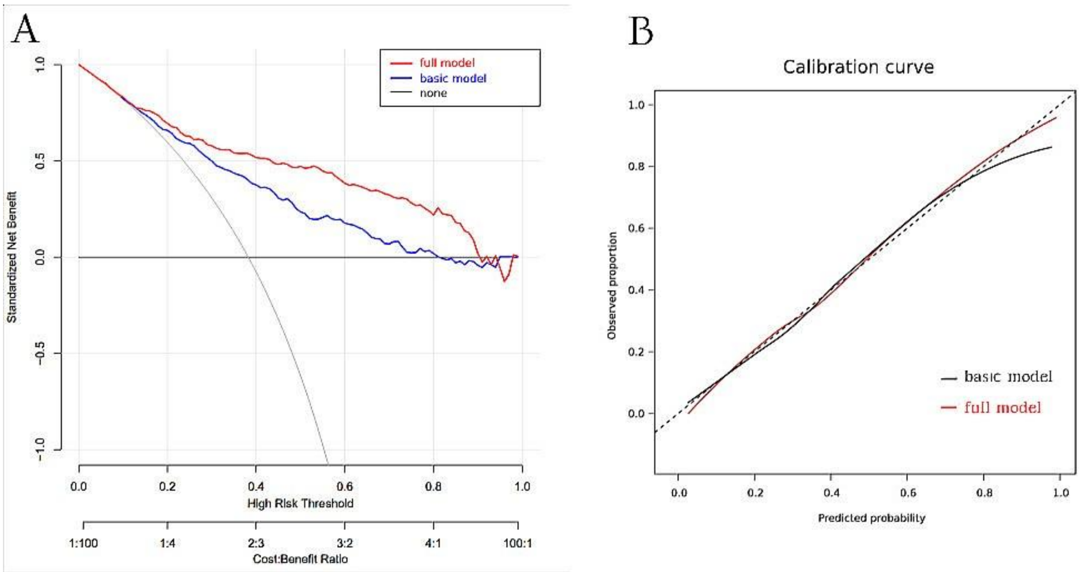

Figure 4 The A plot represents the decision curve analysis (DCA), while the B plot represents the calibration curve.

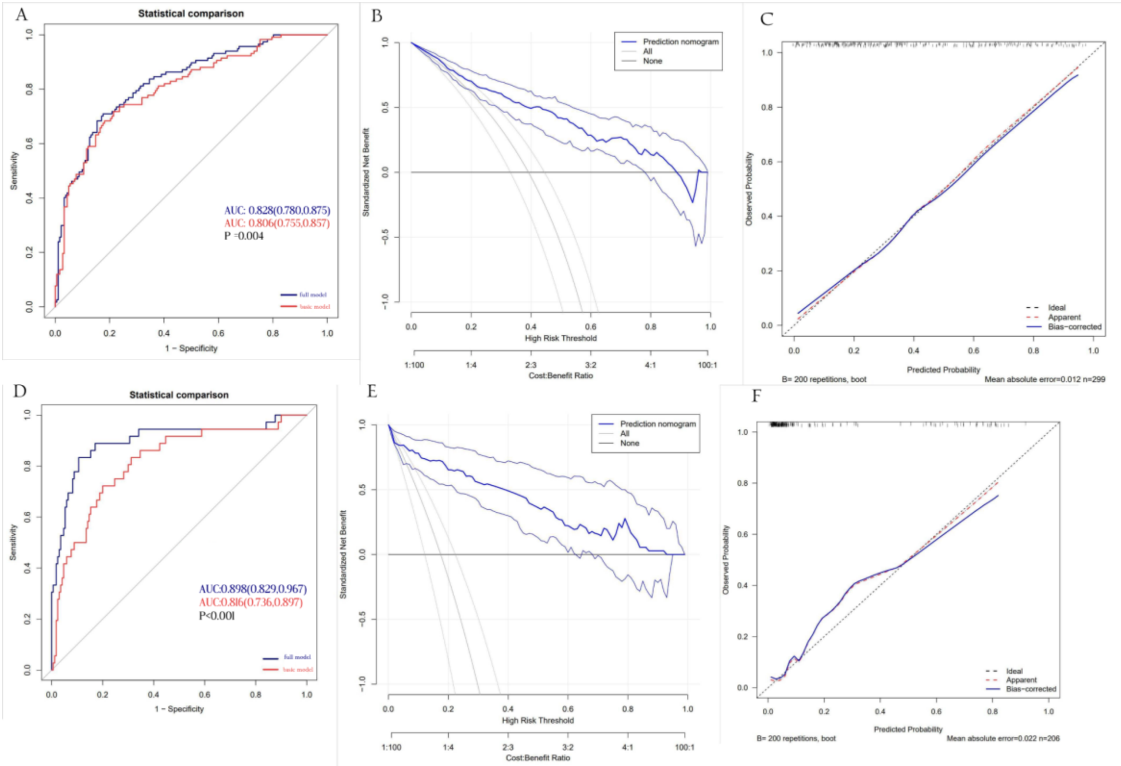

Figure 5 Pictures A, B, and C represent Jieyang People's Hospital, while pictures D, E, and F represent Central Hospital.

Validation Cohort

The demographic and clinical characteristics of the 505 patients from two centers in the validation cohort are presented in Table 3. NIHSS upon admission showed a strong correlation with patient prognosis. In the dataset from Jieyang People's Hospital, the OR was 1.08 (95% CI, 1.04–1.11), and in the dataset from the Affiliated Shantou Hospital of Sun Yat-sen University, the OR was 1.2 (95% CI, 1.04–1.38). This correlation remained significant even after adjusting for other independent risk factors. Adding NIHSS to the basic model improved the overall performance, with the AUC increasing from 0.806 (95% CI, 0.755–0.857) to 0.828 (95% CI, 0.780–0.875) in the dataset from Jieyang People's Hospital, and from 0.816 (95% CI, 0.736–0.897) to 0.898 (95% CI, 0.829–0.967) in the dataset from the Affiliated Shantou Hospital of Sun Yat-sen University (Figure 5A&D). The calibration and DCA curves demonstrated good consistency between the predict

Table3. Differences between with favorable prognosis group and the unfavorable prognosis group in the validation cohort.

Characteristic	Jieyang People's Hospital of Sun Yat-sen University			the Affiliated Shantou Hospital of Sun Yat-sen University		
	Favorable prognosis (n = 182)	Unfavorable prognosis (n = 117)	*P*-Value	Favorable prognosis (n = 170)	Unfavorable prognosis (n = 36)	*P*-Value
Sex (male), n%	77 (42.3)	40 (34.2)	0.046	79 (46.5)	19 (52.8)	0.491
Age (year), mean±SD	57.0 ± 11.8	61.5 ± 12.8	0.425	56.5 ± 11.1	61.2 ± 10.7	**0.022**
Hypertension, n%	84 (46.2)	66 (56.4)	0.688	55 (32.4)	13 (36.1)	0.663
mFS grade, n%			0.048			**<0.001**
0	3 (1.6)	0 (0)		0 (0)	0 (0)	
1	23 (12.6)	1 (0.9)		51 (30)	2 (5.6)	
2	34 (18.7)	8 (6.8)		72 (42.4)	6 (16.7)	

3	20 (11)	62 (53)		25 (14.7)	10 (27.8)	
4	102 (56)	46 (39.3)		22 (12.9)	18 (50)	
Hunt-Hess grade, n%			0.038			**<0.001**
1	37 (20.3)	5 (4.3)		37 (21.8)	2 (5.6)	
2	72 (39.6)	13 (11.1)		84 (49.4)	2 (5.6)	
3	60 (33)	30 (25.6)		34 (20)	7 (19.4)	
4	13 (7.1)	50 (42.7)		14 (8.2)	21 (58.3)	
5	0 (0)	19 (16.2)		1 (0.6)	4 (11.1)	
Level on GCS score, n%			0.068			**<0.001**
Severe (3–8 points)	119 (65.4)	24 (20.5)		15 (8.8)	26 (72.2)	
Moderate (9–12 points)	47 (25.8)	25 (21.4)		15 (8.8)	2 (5.6)	
Mild (13–15 points)	16 (8.8)	68 (58.1)		140 (82.4)	8 (22.2)	
NIHSS score	5.7 ± 9.4	13.8 ± 12.9	<0.001	4.5 ± 9.6	27.4 ± 13.3	**<0.001**
SAP, mmHg	154.4 ± 24.9	161.6 ± 29.9	0.934	147.6 ± 25.7	141.9 ± 29.7	0.237
DAP, mmHg	89.9 ± 15.8	92.6 ± 15.0	0.816	84.9 ± 12.6	81.5 ± 15.6	0.157
Blood glucose, mmol/L	8.8 ± 2.8	10.2 ± 4.0	<0.001	8.2 ± 2.3	9.6 ± 2.3	**<0.001**
Serum calcium level, mmol/L	2.2 ± 0.1	2.2 ± 0.1	0.798	2.3 ± 0.1	2.3 ± 0.1	0.508
Leukocyte count, 10^9/L	10.0 ± 3.9	13.2 ± 4.6	<0.001	10.8 ± 4.5	13.3 ± 5.5	**0.045**
Neutrophil count, 10^9/L	12.5 ± 3.9	16.2 ± 4.8	<0.001	13.5 ± 7.4	16.1 ± 5.8	**0.005**
Lymphocyte count, 10^9/L	1.9 ± 1.3	1.9 ± 1.2	0.688	1.6 ± 1.0	1.8± 1.1	0.274
Platelet count, 10^9/L	240.9 ± 67.4	255.5 ± 75.6	0.083	240.1 ± 69.6	266.1± 81.2	**0.049**

Discussion

The results of the current study revealed that NIHSS is a potential independent predictor for the unfavorable prognosis of aSAH and has advantageous predictive value over other predictors, including the GCS, mFS, and HH scores. The likelihood of a worse prognosis increases with a higher score on the NIHSS.

Although many predictive models for aSAH prognosis have been established, they are limited in terms of convenience, reliability, and accuracy[29-31]. The NIHSS has a stronger predictive ability than other commonly used clinical scales, including the GCS, HH, and mFS scores. The GCS and HH are unable to identify minor neurological deficits. Patients with mild SAH have no focal deficits (only headache), whereas most of them have focal oculomotor nerve dysfunction (or dysfunction of other cranial nerves) and rarely have focal weakness or deficits (unless there is a hematoma affecting the corticospinal tract). The NIHSS score includes items such as visual field and facial palsy, which can reflect subtle deficits and allow them to be treated in a timely manner, while the GCS and HH cannot assess mild neurological deficits. In severe cases, the NIHSS can effectively evaluate a decrease in consciousness and has more grading levels compared to the other scales. The mFS can predict the patient prognosis in patients with aSAH, but requires a CT scan. In contrast, the NIHSS can effectively highlight subtle neurological deficits and does not require additional examinations, making it possible to evaluate the patient immediately upon admission.

The NIHSS is widely used for assessing patients with ischemic stroke and as a monitoring tool for intracerebral hemorrhage[32-36]. In a previous study by Leira et al., the NIHSS was demonstrated to be a powerful predictor of low-grade aneurysm, but excluded POOL-grade subarachnoid aneurysms (i.e., WFNS grade 4/5 aneurysms). In contrast, the present study did not exclude patients with POOL-grade aneurysms and validated the performance of the NIHSS in two independent cohorts, thereby expanding its use to patients with aSAH. In another study, Smith et al. reported a strong association between the NIHSS score and mortality in SAH patients[15]. They used a model that contained the NIHSS as the only predictor and obtained an AUC of 0.84. Our results were similar to theirs, with an AUC of 0.806 indicating that the NIHSS is a reliable predictor of aSAH outcomes. The results of this study are based on a large dataset, but they were limited by the fact that some patients had missing NIHSS data[18]. Our study included all patients with aSAH and had a low rate of missing NIHSS.

The pathophysiological mechanisms underlying the association between the NIHSS score and the prognosis for patients with aSAH have not been well elucidated. However, we can propose several possible explanations. First, the NIHSS score may reflect the severity of bleeding and brain injury, which have direct impacts on the illness's outcomes[37]. In ischemic stroke patients, the NIHSS score was negatively correlated with the prognosis, which might be because higher NIHSS scores indicated larger infarct volume, more severe ischemia, and more extensive brain damage[37]. In hemorrhagic stroke patients, the relationship between the NIHSS score and the prognosis might be related to factors such as hemorrhage severity, brain injury, and blood pressure variability[32]. We speculated that, in aSAH patients, higher NIHSS scores might represent larger hematoma or acute obstructive hydrocephalus, leading to more severe neurological deficits. Another study reported that the presence of cranial nerve palsy was an independent predictor of cerebral infarction and was associated with poorer outcomes in tuberculous meningitis patients[38]. We hypothesized that in mild aSAH patients, who might only present with mild headache or cranial nerve deficit symptoms, the NIHSS could detect subtle signs of ocular movement (oculomotor nerve), facial palsy (facial nerve), and visual field defect (optic nerve), thus providing more comprehensive information for disease assessment.

Along with the NIHSS score, several other risk factors, including age and leukocyte count, were independently associated with the mRS score at 3 months. Advanced age has consistently been identified as an independent factor associated with poor outcomes[39-41]. Therefore, factoring in age is imperative when assessing the prognosis of individual patients and comparing the efficacy of various treatment and management modalities[42,43]. A higher leukocyte count at admission has been associated with poor outcomes in SAH patients. Mahta et al. showed that early monitoring of the leukocyte count could predict the prognosis in patients with aSAH. However, they included leukocyte counts within the first 5 days of admission, whereas in the present study, the leukocyte count at admission was used, which could minimize the potential influence of subsequent infections and more accurately reflect the immune inflammatory response caused by SAH, thus enhancing the predictive ability[10,11].

Limitations

There were several limitations in our study. First, the retrospective design of the study meant that the data had already been collected. While the use of three independent cohorts may have helped to reduce bias, future prospective multicenter cohort studies are needed to validate the predictive value of the NIHSS score for adverse outcomes. Second, owing to the constraints of our data, we were unable to gather other indicators that could potentially impact patient outcomes. This includes important elements like the WFNS and Yasargil SAH grading scales, which play a crucial role in assessing the condition of patients with subarachnoid hemorrhage. Additionally, parameters such as cerebrospinal fluid drainage, lumbar puncture, complications, and delayed cerebral ischemia, all of which can significantly influence patient prognosis, were not collected. The NIHSS, while valuable for stroke evaluation, does not fully capture SAH-specific prognostic factors such as aneurysm complexity, rebleeding risk, or hydrocephalus. Its use here as an adjunctive tool may have introduced gaps in outcome prediction. We earnestly hope to rectify these shortcomings in our future research endeavors.

CONCLUSION

The NIHSS score is a potential independent predictor of poor outcome in patients with aSAH. NIHSS upon admission could be a convenient tool for clinicians to gain early prediction of clinical outcomes in patients with aneurysmal SAH.

Disclosure of conflicts of interest: The authors declare no financial or other conflicts of interest.

Patient consent for publication: Not required.

Data availability statement: Data are available upon request.

Ethics statement: The study was approved by the Ethics Committees of the First Affiliated Hospital of Shantou University Medical College (No: B-2021-244).

Author Contribution Statement : The authors confirm contribution to the paper as follows: Study conception and design: Gengyu Chen, Yuan Zhong, and Huibin Kang ; Data collection: Gengyu Chen, Yuan Zhong, and Dongzhou Zhuang; Analysis and interpretation of results: Gengyu Chen, Yuan Zhong; Draft manuscript preparation: Gengyu Chen, Huibin Kang. All authorsreviewed the results and approved the final version of the manuscript.

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