




# A 90-Day Prognostic Model Based on the Early Brain Injury Indicators after Aneurysmal Subarachnoid Hemorrhage: the TAPS Score

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## Abstract

This study aimed to establish a new scoring model based on the early brain injury (EBI) indicators to predict the 90-day functional outcomes in patients with aneurysmal subarachnoid hemorrhage (aSAH). We retrospectively enrolled 825 patients and prospectively enrolled 108 patients with aSAH who underwent surgical clipping or endovascular coiling (derivation cohort = 640; validation cohort = 185; prospective cohort = 108) in our institute. We established a logistic regression model based on independent risk factors associated with 90-day unfavorable outcomes. The discrimination of the prognostic model was assessed by the area under the curve in a receiver operating characteristic curve analysis. The Hosmer–Lemeshow goodness-of-fit test and a calibration plot were used to evaluate the calibration of the prediction model. The developed scoring model named “TAPS” (total score, 0–7 points) included the following admission variables: age > 55 years old, WFNS grade of 4–5, mFS grade of 3–4, Graeb score of 5–12, white blood cell count >  $11.28 \times 10^9/L$ , and surgical clipping. The model showed good discrimination with the area under the curve in the derivation, validation, and prospective cohorts which were 0.816 ( $p < 0.001$ , 95%CI = 0.77–0.86), 0.810 ( $p < 0.001$ , 95%CI = 0.73–0.90), and 0.803 ( $p < 0.001$ , 95%CI = 0.70–0.91), respectively. The model also demonstrated good calibration (Hosmer–Lemeshow goodness-of-fit test:  $X^2 = 1.75$ ,  $df = 8$ ,  $p = 0.988$ ). Compared with other predictive models, TAPS is an easy handle tool for predicting the 90-day unfavorable outcomes of aSAH patients, which can help clinicians better understand the concept of EBI and quickly identify those patients at risk of poor prognosis, providing more positive treatment strategies. Trial registration: NCT04785976. Registered 5 March 2021-retrospectively registered, <http://www.clinicaltrials.gov>.

**Keywords** Aneurysmal subarachnoid hemorrhage · Model · Early brain injury · Functional outcome

## Introduction

The concept of “early brain injury” (EBI) was introduced in a rat model in 2004 to explain the acute pathophysiological events that occur in the brain within the first 72 h of

aneurysmal subarachnoid hemorrhage (aSAH) [1]. EBI is now believed to be an important determinant of unfavorable outcomes in patients with aSAH [2–6].

The first 72 h after aneurysm rupture are critical for patients, and most patients die within this dangerous period.

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At this stage, patients experience brain injuries due to blood release and accumulation, acute reactive hyperemia, transient cerebral ischemia, and systemic complications [7–9]. Moreover, these brain injuries can also increase the risk of complications in various body systems, resulting in a poor prognosis for the patient [10, 11]. At present, the definition of the EBI indicator is not clear, thus leading to a dilemma that although people know the criticality of EBI, the indicators cannot be effectively used in clinical practice. A recent review attempted to define EBI from the perspectives of four fields: clinical signs and symptoms, neuroimaging, invasive neuromonitoring, and neurohemoinflammation and systemic inflammation, which inspired us to explore the practical clinical application value of EBI [12].

Therefore, based on the definition of EBI, in this study, we aimed to (1) evaluate the relationship between EBI indicators and 90-day prognosis, (2) devise a new scoring system for aSAH patients based on EBI indicators that can intuitively evaluate their prognosis, and (3) compare EBI model with already published models to evaluate the advantages of EBI model comprehensively. The results will help clinicians better understand this critical period, improve their ability to perceive EBI indicators, identify those patients at risk early, and provide more positive treatment strategies.

## Methods

### Study Design

A total of 825 consecutive aSAH patients who underwent surgical clipping (SC) or endovascular coiling (EC) were retrospectively enrolled and divided into two independent cohorts (derivation cohort,  $n=640$ , January 2015 to December 2019 and validation cohort,  $n=185$ , January 2020 to December 2020). Furthermore, another independent cohort (prospective cohort,  $n=108$ ) was enrolled between April 2021 and September 2021. All patient data were from the Long-term Prognosis of Emergency Aneurysmal Subarachnoid Hemorrhage (LongTEAM) Registry study (registration no. NCT 04,785,976). In this study, all patients had angiographically documented aneurysms with subarachnoid hemorrhage (SAH), confirmed by either computed tomography (CT) or lumbar puncture. We set the inclusion criteria as follows: (1) age  $\geq 18$  years; (2) less than 72 h from the rupture to the admission and less than 72 h from the admission to treatment; (3) single aneurysm; and (4) complete 90-day follow-up. The main exclusion criteria were as follows: (1) previous history of ruptured aneurysm or SAH; (2) physical disability due to any previous disease; (3) treatment including external ventricular drainage, lumbar puncture, angiography, intubation, and/or mechanical ventilation at other hospitals before presentation to our hospital; and (4)

missing data, including medical, radiological, and laboratory information. All available data without missing essential values from databases were used to meet the ten events per variable rule and maximize the generalizability and power of our results.

This study was approved by the Institutional Review Board of Beijing Tiantan Hospital (KY 2021–008-01). Informed consent was obtained from all individual participants or their authorized representatives for the study. All patients were managed according to the guidelines during hospitalization [13].

### Parameters

All patients' data were obtained from their medical records. We collected patients' demographic information, medical history, size and location of the aneurysm, EBI indicators, and in-hospital complications. EBI indicators included clinical symptoms and consciousness scores on admission, first imaging characteristics and scores, and laboratory examination on admission. Clinical signs and condition of consciousness scores included early seizures and early loss of consciousness after ictus and the World Federation of Neurosurgical Societies (WFNS) grade [14]. Imaging characteristics and scores included acute hydrocephalus, the modified Fisher scale grade (mFS), the Graeb score, and the Subarachnoid Hemorrhage Early Brain Edema (SEBES) score [15–17]. The patient's radiographic scores were assessed independently by two neurosurgeons, and a third radiologist would determine the final result in case of controversial results. Laboratory examination included the glucose level (GLU, fasting plasma glucose normal range: [3.9–6.1] mmol/L), white blood cell (WBC, normal range: [3.5–9.5]  $\times 10^9/L$ ) count, monocyte (MONO, normal range: [0.10–0.60]  $\times 10^9/L$ ) count, lymphocyte (LY, normal range: [1.10–3.2]  $\times 10^9/L$ ) count, neutrophil (NEUT, normal range: [1.80–6.30]  $\times 10^9/L$ ) count, and hemoglobin (HGB, normal range: [120–160 for male; 110–150 for female] g/L) level. Besides, we collected some ratio-related biomarkers that have been previously reported to be associated with prognosis, such as serum glucose/potassium ratio (GLU/K), neutrophil-to-lymphocyte ratio (NLR), mean platelet volume-to-platelet count ratio (MPV/PLT), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) [18–22]. In-hospital complications such as delayed cerebral ischemia (DCI), intracranial infection, hypoproteinemia, pneumonia, and deep vein thrombosis were also collected. Supplementary Table 1 shows the detailed diagnostic criteria for the above in-hospital complications.

## Outcome Measures

The neurosurgeon followed up with patients via telephone or an outpatient appointment 90 days after discharge. Unfavorable outcome was defined as an mRS score  $\geq 3$ .

## Statistical Analysis

All statistical analyses were performed using SPSS Statistics 26.0 (IBM, Armonk, New York, USA), GraphPad PRISM 8.3.0. (GraphPad Software Inc, San Diego, CA, USA), and R (version 2.12.2) software for Windows.  $p < 0.05$  was considered statistically significant.

Descriptive variables were summarized as the mean  $\pm$  standard deviation (SD) or median values with interquartile range (IQR) for continuous variables and frequencies (percentage) for categorical variables. Chi-squared tests or Fisher's exact tests were used to compare categorical variables, and Student's *t*-test or the Mann–Whitney test was used to compare the quantitative variables, as appropriate. Weighted kappa coefficients were used to test inter-rater agreement of imaging features (Supplementary Table 2). Only variables with  $p \leq 0.05$  in univariate analysis were entered in multivariate logistic regression analysis (forward stepwise) to identify the independent EBI risk factors associated with 90-day unfavorable outcomes. Associations were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). If there were continuous variables in the multivariate output results, the cutoff value was calculated by Youden's index through receiver operating characteristic curve (ROC) analysis and reanalyzed into the multivariate regression model as new variables to obtain the final result. Multicollinearity was assessed using the tolerance and variance inflation factor (VIF).

We computed a prediction equation for 90-day unfavorable functional outcome in aSAH patients based on each risk factor's  $\beta$  coefficients in the multivariate analysis, referring to the following Eq. (1):

$$P = \frac{1}{1 - e^{-LP}} \quad (1)$$

with  $LP = a + b_1X_1 + b_2X_2 + \dots + b_pX_p$ ,  $b_1, b_2, \dots, b_p$  as the regression coefficients associated with each of the variables in the final logistic model [23]. Considering the utility and convenience of clinical application, we developed a new EBI risk-scoring system based on the  $\beta$  coefficients, and the ability of the model to discriminate was assessed by the area under the curve (AUC) in ROC analysis. Prediction accuracy was evaluated using Brier scores. The Hosmer–Lemeshow goodness-of-fit test and a calibration plot were used to evaluate the calibration of the prediction model.

## Results

### Patient Cohort

A total of 933 patients were included in the study, of whom 640 patients were included in the derivation cohort, 185 patients were included in the validation cohort, and 108 patients were included in the prospective cohort. The characteristics of the derivation, validation, and prospective cohorts are summarized in Tables 1 and 2. The 90-day unfavorable outcome rate was 17.5% (112/640) in the derivation cohort, 20.5% (38/185) in the validation cohort, and 15.7% (17/108) in the prospective cohort.

### Independent Risk Factors Associated with 90-Day Unfavorable Outcomes in the Derivation Cohort

The forward stepwise multivariate analysis showed that age ( $p < 0.001$ ,  $OR = 1.05$ ,  $95\%CI = 1.02–1.07$ ), WFNS grade of 4–5 ( $p < 0.001$ ,  $OR = 4.32$ ,  $95\%CI = 2.59–7.19$ ), mFS grade of 3–4 ( $p = 0.014$ ,  $OR = 3.05$ ,  $95\%CI = 1.25–7.40$ ), Graeb score of 5–12 ( $p = 0.008$ ,  $OR = 2.56$ ,  $95\%CI = 1.28–5.09$ ), WBC count ( $p = 0.009$ ,  $OR = 1.08$ ,  $95\%CI = 1.02–1.14$ ), and surgical clipping ( $p = 0.005$ ,  $OR = 2.00$ ,  $95\%CI = 1.24–3.23$ ) were independent risk factors associated with 90-day unfavorable outcomes (Supplementary Table 3). ROC analysis was conducted for the two continuous variables (age and WBC count), and the cutoff value was determined by Youden's index (age  $> 55$ ,  $p < 0.001$ , sensitivity = 64.3%, specificity = 58.3%, Youden's index = 0.23; WBC count  $> 11.28 \times 10^9/L$ ,  $p < 0.001$ , sensitivity = 83.0%, specificity = 46.8%, Youden's index = 0.30).

Two indicators (age  $> 55$  and WBC count  $> 11.28 \times 10^9/L$ ) were returned to the multivariate model to derive the final results. The model demonstrated that age  $> 55$  years old ( $p < 0.001$ ,  $OR = 2.51$ ,  $95\%CI = 1.55–4.05$ ), WFNS grade of 4–5 ( $p < 0.001$ ,  $OR = 4.44$ ,  $95\%CI = 2.70–7.32$ ), mFS grade of 3–4 ( $p = 0.011$ ,  $OR = 3.17$ ,  $95\%CI = 1.31–7.71$ ), Graeb score of 5–12 ( $p = 0.007$ ,  $OR = 2.58$ ,  $95\%CI = 1.30–5.13$ ), WBC count  $> 11.28 \times 10^9/L$  ( $p < 0.001$ ,  $OR = 2.81$ ,  $95\%CI = 1.59–4.98$ ), and surgical clipping ( $p = 0.007$ ,  $OR = 1.94$ ,  $95\%CI = 1.20–3.14$ ) were independent risk factors associated with 90-day unfavorable outcomes (Table 3). There was no evidence of multicollinearity between risk factors, with tolerance values above 0.10 and VIF values  $< 10$  in all cases (Supplementary Table 2).

### Model Performance

We constructed a new EBI scoring system based on the model output results, named the Tiantan Aneurysmal

**Table 1** Pre-operative information in derivation, validation, and prospective cohort

Pre-operative information				
Patient characteristics	Derivation cohort	Validation cohort	<i>p</i>	Prospective cohort
No. of patients	640	185		108
Female, <i>n</i> (%)	371 (58.0)	108 (58.4)	0.921	70 (64.8)
Age, years, mean ± SD	54.3 ± 11.0	56.2 ± 11.1	0.037	56.6 ± 12.6
Hypertension, <i>n</i> (%)	393 (61.4)	106 (57.3)	0.314	52 (48.1)
Hyperlipidemia, <i>n</i> (%)	60 (9.4)	13 (7.0)	0.322	3 (2.8)
Diabetes mellitus, <i>n</i> (%)	69 (10.8)	12 (6.5)	0.084	8 (7.4)
Heart disease, <i>n</i> (%)	52 (8.1)	13 (7.0)	0.625	7 (6.5)
Posterior circulation, <i>n</i> (%)	64 (10.0)	22 (11.9)	0.458	17 (15.7)
Maximum diameter of aneurysm <sup>a</sup> , mean ± SD	6.63 ± 5.96	6.79 ± 4.97	0.771	6.30 ± 3.92
Early seizures, <i>n</i> (%)	43 (6.7)	7 (3.8)	0.141	2 (1.9)
Early loss of consciousness, <i>n</i> (%)	193 (30.2)	55 (29.7)	0.911	36 (33.3)
WFNS grade 4–5, <i>n</i> (%)	136 (21.3)	42 (22.7)	0.672	28 (25.9)
mFS grade 3–4, <i>n</i> (%)	492 (76.9)	151 (81.6)	0.170	43 (39.8)
Graeb score 5–12, <i>n</i> (%)	52 (8.1)	19 (10.3)	0.360	10 (9.3)
SEBES score 3–4, <i>n</i> (%)	321 (50.2)	82 (44.3)	0.162	57 (52.8)
Acute hydrocephalus, <i>n</i> (%)	258 (40.3)	73 (39.5)	0.835	33 (30.6)
Glucose <sup>b</sup> , median (IQR)	7.62 (6.65–8.94)	7.67 (6.71–9.01)	0.477	7.62 (6.57–8.88)
White blood cell count <sup>c</sup> , median (IQR)	12.32 (9.66–15.54)	12.31 (9.63–15.17)	0.941	12.55 (10.17–14.90)
Monocyte count <sup>c</sup> , median (IQR)	0.40 (0.27–0.56)	0.42 (0.27–0.59)	0.357	0.37 (0.26–0.51)
Lymphocyte count <sup>c</sup> , median (IQR)	0.98 (0.69–1.38)	0.93 (0.72–1.31)	0.839	0.90 (0.65–1.19)
Neutrophil count <sup>c</sup> , median (IQR)	10.89 (8.30–13.84)	10.75 (8.10–13.47)	0.829	11.19 (8.79–13.74)
Hemoglobin <sup>d</sup> , median (IQR)	141.0 (130.0–150.8)	140.0 (129.0–150.5)	0.776	139.5 (130.3–149.0)
GLU/K, median (IQR)	2.00 (1.68–2.47)	2.01 (1.68–2.46)	0.707	2.02 (1.72–2.58)
NLR, median (IQR)	11.60 (7.25–16.77)	11.51 (7.54–18.17)	0.853	12.34 (8.38–19.09)
MPV/PLT, median (IQR)	0.04 (0.04–0.05)	0.04 (0.03–0.05)	0.425	0.04 (0.03–0.05)
PLR, median (IQR)	228.4 (165.2–311.0)	222.0 (163.0–318.3)	0.761	260.7 (172.4–380.6)
MLR, median (IQR)	0.38 (0.27–0.57)	0.40 (0.27–0.61)	0.473	0.39 (0.28–0.56)
Treatment modality			0.247	
Surgical clipping, <i>n</i> (%)	325 (50.8)	85 (45.9)		52 (48.1)
Endovascular coiling, <i>n</i> (%)	315 (49.2)	100 (54.1)		56 (51.9)

WFNS, world federation of neurological societies; mFS, modified Fisher; SEBES, subarachnoid hemorrhage early brain edema score; mRS, modified rankin scale; GLU/K, serum glucose/potassium ratio; NLR, neutrophil-to-lymphocyte ratio; MPV/PLT, mean platelet volume-to-platelet count ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio. <sup>a</sup>Unit of measurement: mm; <sup>b</sup>unit of measurement: mmol/L; <sup>c</sup>unit of measurement: 10<sup>9</sup>/L; <sup>d</sup>unit of measurement: g/L

**Table 2** Post-operative information in derivation, validation, and prospective cohort

Post-operative information				
In-hospital complications and outcomes	Derivation cohort	Validation cohort	<i>p</i>	Prospective cohort
Delayed cerebral ischemia, <i>n</i> (%)	176 (27.5)	46 (24.9)	0.477	26 (24.1)
Intracranial infection, <i>n</i> (%)	74 (11.6)	18 (9.7)	0.486	18 (16.7)
Hypoproteinemia, <i>n</i> (%)	230 (35.9)	53 (28.6)	0.066	39 (36.1)
Pneumonia, <i>n</i> (%)	185 (28.9)	68 (36.8)	0.041	38 (35.2)
Deep vein thrombosis, <i>n</i> (%)	51 (8.0)	19 (10.3)	0.322	8 (7.4)
mRS 3–6 at 90 days, <i>n</i> (%)	112 (17.5)	38 (20.5)	0.345	17 (15.7)

**Table 3** Pre-operative risk factors in the derivation cohort after univariate and multivariate analysis

Variables	Univariate			Multivariate		
	mRS 0–2 ( <i>n</i> = 528)	mRS 3–6 ( <i>n</i> = 112)	<i>p</i>	OR (95%CI)	<i>p</i>	OR (95%CI)
Female, <i>n</i> (%)	304 (57.6)	67 (59.8)				
Age > 55, <i>n</i> (%)	220 (41.7)	72 (64.3)	< 0.001	2.52 (1.65–3.85)	< 0.001	2.51 (1.55–4.05)
Hypertension, <i>n</i> (%)	315 (59.7)	78 (69.6)	0.050	1.55 (1.00–2.41)		
Hyperlipidemia, <i>n</i> (%)	54 (10.2)	6 (5.4)				
Diabetes mellitus, <i>n</i> (%)	52 (9.8)	17 (15.2)				
Heart disease, <i>n</i> (%)	41 (7.8)	11 (9.8)				
Posterior circulation, <i>n</i> (%)	57 (10.8)	7 (6.3)				
Maximum diameter of aneurysm <sup>a</sup> , mean ± SD	6.52 ± 6.23	7.18 ± 4.36				
Early seizures, <i>n</i> (%)	31 (5.9)	12 (10.7)				
Early loss of consciousness, <i>n</i> (%)	134 (25.4)	59 (52.7)	< 0.001	3.27 (2.15–4.98)		
WFNS grade 4–5, <i>n</i> (%)	74 (14.0)	62 (55.4)	< 0.001	7.61 (4.87–11.89)	< 0.001	4.44 (2.70–7.32)
mFS grade 3–4, <i>n</i> (%)	386 (73.1)	106 (94.6)	< 0.001	6.50 (2.79–15.13)	0.011	3.17 (1.31–7.71)
Graeb score 5–12, <i>n</i> (%)	27 (5.1)	25 (22.3)	< 0.001	5.33 (2.96–9.62)	0.007	2.58 (1.30–5.13)
SEBES score 3–4, <i>n</i> (%)	256 (48.5)	65 (58.0)				
Acute hydrocephalus, <i>n</i> (%)	202 (38.3)	56 (50.0)	0.022	1.61 (1.07–2.43)		
Glucose <sup>b</sup> , median (IQR)	7.47 (6.52–8.69)	8.71 (7.06–10.27)	< 0.001	1.24 (1.14–1.35)		
White blood cell count <sup>c</sup> > 11.28, <i>n</i> (%)	281 (53.2)	93 (83.0)	< 0.001	4.30 (2.55–7.25)	< 0.001	2.81 (1.59–4.98)
Monocyte count <sup>c</sup> , median (IQR)	0.39 (0.26–0.54)	0.46 (0.31–0.73)	< 0.001	5.67 (2.68–12.00)		
Lymphocyte count <sup>c</sup> , median (IQR)	0.99 (0.69–1.36)	0.98 (0.66–1.45)				
Neutrophil count <sup>c</sup> , median (IQR)	10.33 (7.97–13.40)	12.85 (10.52–15.27)	< 0.001	1.14 (1.08–1.19)		
Hemoglobin <sup>d</sup> , median (IQR)	140.0 (130.0–150.0)	144.0 (129.5–155.8)				
GLU/K, median (IQR)	1.96 (1.66–2.33)	2.45 (1.77–3.02)	< 0.001	1.96 (1.52–2.52)		
NLR, median (IQR)	10.95 (6.96–15.70)	14.29 (8.73–19.92)	0.038	1.01 (1.00–1.03)		
MPV/PLT, median (IQR)	0.04 (0.04–0.05)	0.04 (0.03–0.05)	0.045	0.24 (0.06–0.97)		
PLR, median (IQR)	226.2 (164.4–304.7)	259.6 (167.9–393.6)				
MLR, median (IQR)	0.37 (0.26–0.53)	0.51 (0.35–0.65)	< 0.001	4.16 (1.93–9.00)		
Surgical clipping, <i>n</i> (%)	255 (48.3)	70 (62.5)	0.007	1.78 (1.17–2.71)	0.007	1.94 (1.20–3.14)

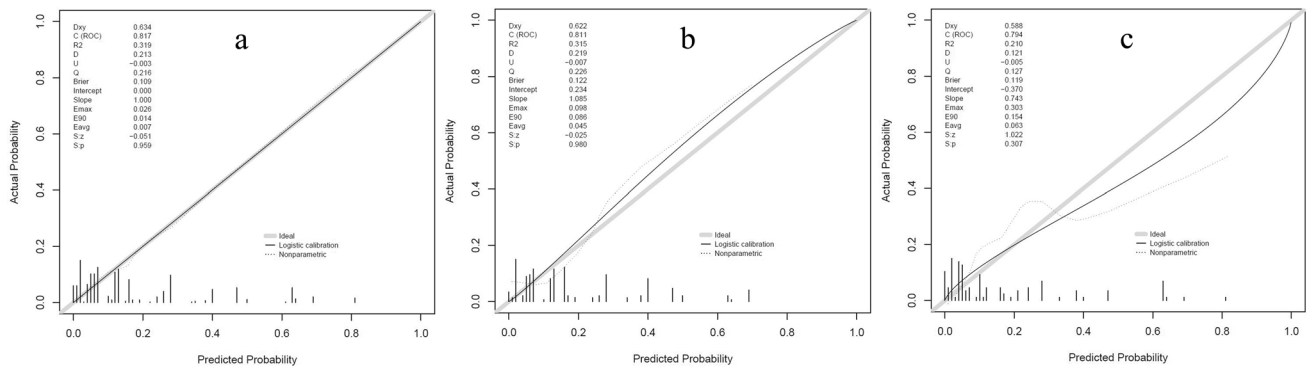
mRS, modified Rankin scale; OR, odds ratio; CI, confidence interval; WFNS, world federation of neurological societies; mFS, modified Fisher; SEBES, subarachnoid hemorrhage early brain edema score; GLU/K, serum glucose/potassium ratio; NLR, neutrophil-to-lymphocyte ratio; MPV/PLT, mean platelet volume-to-platelet count ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio. <sup>a</sup>Unit of measurement: mm; <sup>b</sup>unit of measurement: mmol/L; <sup>c</sup>unit of measurement: 10<sup>9</sup>/L; <sup>d</sup>unit of measurement: g/L

Subarachnoid Hemorrhage Prognostic Scoring System (TAPS), that allowed for the estimation of 90-day unfavorable outcomes in patients with aSAH, according to Eq. (1), where  $LP = -4.714 + 0.919 \times (\text{age} > 55 \text{ years old} = \text{yes}) + 1.491 \times (\text{WFNS grade} = 4-5) + 1.155 \times (\text{mFS grade} = 3-4) + 0.947 \times (\text{Graeb score} = 5-12) + 1.033 \times (\text{WBC} > 11.28 \times 10^9/\text{L} = \text{yes}) + 0.664 \times (\text{surgical clipping} = \text{yes})$ . The AUC for this equation in the derivation, validation, and prospective cohort was 0.817, 0.811, and 0.794, respectively. The calibration plot also revealed a good concordance between the likelihood of predicted unfavorable outcome and actual unfavorable outcome in the derivation cohort (Brier = 0.109), validation cohort (Brier = 0.122), and prospective cohort (Brier = 0.119) (Fig. 1).

Based on the  $\beta$  coefficients in the multivariate analysis, scores of 2 were assigned to a WFNS grade of 4–5

and scores of 1 were assigned to age > 55 years old, mFS grade of 3–4, Graeb score of 5–12, WBC > 11.28 × 10<sup>9</sup>/L, and surgical clipping. The total score of the scoring system was 7 (range 0–7) points to predict the functional outcome of patients with aSAH 90 days after discharge (Table 4). In the derivation cohort, the AUC of the TAPS was 0.816 ( $p < 0.001$ , 95%CI = 0.772–0.859), which showed good calibration (Hosmer–Lemeshow goodness-of-fit test:  $X^2 = 1.75$ ,  $df = 8$ ,  $p = 0.988$ ). In the validation and prospective cohort, the AUC of the TAPS was 0.810 ( $p < 0.001$ , 95%CI = 0.725–0.896) and 0.803 ( $p < 0.001$ , 95%CI = 0.698–0.907) (Fig. 2).

When TAPS ranges from 6 to 7, the prediction risk of 90-day unfavorable outcomes was 68.1%, 70.0%, and 60.1% in the derivation, validation, and prospective cohort (Fig. 2).



**Fig. 1** Discrimination and calibration according to the equation in the **a** derivation, **b** validation, and **c** prospective cohorts

**Table 4** Tiantan Aneurysmal Subarachnoid Hemorrhage Prognostic Scoring System (TAPS) derived from  $\beta$  coefficients

Risk factors	$\beta$ coefficients	Categories	Scores
Age	0.92	$\leq 55$	0
		$> 55$	1
WFNS	1.50	1–3	0
		4–5	2
mFS	1.16	0–2	0
		3–4	1
Graeb	0.95	0–4	0
		5–12	1
WBC <sup>a</sup>	1.03	$\leq 11.28$	0
		$> 11.28$	1
Surgical clipping	0.66	No	0
		Yes	1
Total scores			7

WFNS, world federation of neurological societies; mFS, modified Fisher; WBC, white blood cell. <sup>a</sup>Unit of measurement:  $10^9/L$

**Comparison of TAPS with other Predictive Models for aSAH Patients**

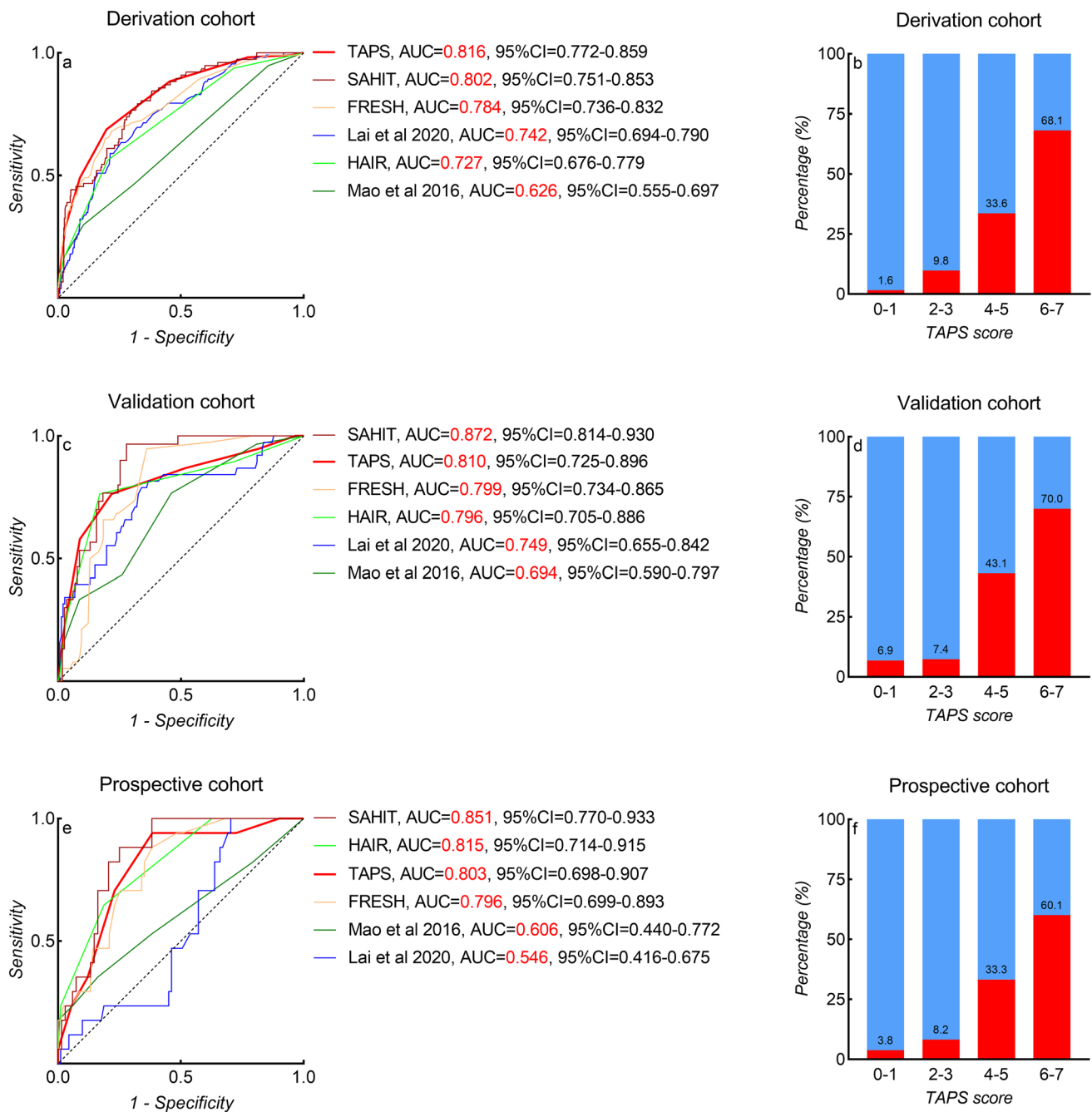
We compared TAPS with five other prediction models (Table 5). TAPS is an easy-to-perform model that contains easily accessible indicators. In the derivation cohort, TAPS shows better discrimination than SAHIT (AUC = 0.802), FRESH (AUC = 0.784), Lai et al. 2020 (AUC = 0.742), HAIR (AUC = 0.727), and Mao et al. 2016 (AUC = 0.626). In the validation cohort, TAPS shows better discrimination than FRESH (AUC = 0.799), HAIR (AUC = 0.796), Lai et al. 2020 (AUC = 0.749), and Mao et al. 2016 (AUC = 0.694). In the prospective cohort, TAPS shows better discrimination than FRESH (AUC = 0.796), Mao et al. 2016 (AUC = 0.606), and Lai et al. 2020 (AUC = 0.546) (Fig. 2).

**Discussion**

Aneurysmal subarachnoid hemorrhage is a life-threatening condition with high disability and mortality rates [24, 25]. The 72-h period after a stroke is critical, and patient deaths are mostly due to EBI mechanisms [1–4, 12]. It is now widely accepted that EBI is a key factor leading to poor patient prognosis and is even more harmful than delayed complications, such as cerebral vasospasm (CVS) and DCI, occurring in the delayed phase [2, 4, 26]. Some abnormal changes in EBI indicators may also be a precursor to CVS and CVS-unrelated DCI, increasing the risk of unfavorable outcomes [17, 27]. From this point of view, controlling EBI is essential for patient prognosis.

Our study provides a prediction model named the “TAPS” based on the EBI indicators to predict unfavorable outcomes at 90 days after discharge in patients with aSAH. The model contains demographic information, clinical symptoms and consciousness scores on admission, first imaging characteristics and scores, laboratory examination on admission, and treatment modality. Finally, the model output results included six factors: age  $> 55$  years old, WFNS grade of 4–5, mFS grade of 3–4, Graeb score of 5–12, WBC count  $> 11.28 \times 10^9/L$ , and surgical clipping. According to the AUC results of the derivation (0.816), validation (0.810), and the prospective cohort (0.803), the TAPS was very stable with good performance in predicting 90-day unfavorable outcomes.

Before our study, some models had been published for the prognosis of patients with aSAH. In 2016, Mao et al. proposed a 3-month prognostic model for elderly aSAH patients, including age, hypertension, frailty, smoking, Hunt and Hess (HH) score, aneurysm number, and aneurysm size; the discrimination of the model in their validation cohort was 0.79 [28]. In 2020, Lai et al. proposed a 3-month prognostic model, including a Glasgow coma scale at 24 h after surgery, surgical clipping, and NLR; the discrimination of the model in their validation cohort was 0.86 [29].



**Fig. 2** Comparison of AUC between TAPS and five other models in the **a** derivation, **c** validation, and **e** prospective cohorts. Probability of TAPS to predict 90-day unfavorable outcomes in the **b** derivation, **d** validation, and **f** prospective cohorts

In 2018, the SAHIT multinational cohort study proposed a 3-month prognostic model, including age, WFNS grade, pre-morbid hypertension, Fisher grade, size and location of the aneurysm, and surgical clipping; the discrimination of the model in their validation cohort was 0.81 [30]. In 2014, Lee et al. proposed a model named “HAIR” to predict in-hospital mortality for SAH patients, including age, HH score, intraventricular hemorrhage (IVH), and rebleed

within 24 h of admission; the highest score of the model could predict 83.3% in-hospital mortality [31]. In 2016, Jens et al. proposed a model named “FRESH” to predict the 12-month outcomes for SAH patients, including age, HH score, APACHE-II score, and rebleed with 48 h of hospital admission; the discrimination of the model in their validation cohort was 0.77 [32]. Our study compared the similarities and differences of TAPS with the above five already

**Table 5** Comparison of information between models. Abbreviations: *mRS*, modified Rankin Scale; *GOS*, Glasgow outcome scale; *Pre-op*, pre-operative; *Post-op*, post-operative; *GCS*, Glasgow coma scale; *WFNS*, world federation of neurological societies; *mFS*, modified Fisher Scale; *WBC*, white blood cell; *HH*, Hunt-Hess grade; *NLR*, neutrophil-to-lymphocyte ratio; *FS*, Fisher Scale; *IVH*, intraventricu-

lar hemorrhage; *APACHE II*, Acute Physiology and Chronic Health Evaluation II. Red, demographic information; orange, clinical status; green, imaging information; gray, medical history; blue, laboratory tests; yellow, a scale includes laboratory tests, demographic information, and medical history; purple, treatment modality

Model	Study patient	Outcome	Difficulty	Timing	Variable							
TAPS	≥ 18y aSAH	3m-mRS (0-2 vs. 3-6)	Easy	Pre-op	Age	WFNS	WBC	Graeb	mFS	Clipping		
Mao et al. 2016	≥ 60y aSAH	3m-mRS (0-2 vs. 3-6)	Normal	Pre-op	Age	HH	Frailty	Hypertension	Smoking	Aneurysm number	Aneurysm size	
Lai et al. 2020	18-80y aSAH	3m-mRS (0-3 vs. 4-6)	Easy	Post-op	GCS	NLR	Clipping					
SAHIT	aSAH	3m-GOS (1-3 vs. 4-5)	Hard	Pre-op	Age	WFNS	Hypertension	FS	Location of aneurysm	Aneurysm size	Clipping	
HAIR	SAH	In-hospital mortality	Easy	pre-op/intra op	Age	HH	IVH	Rebleed				
FRESH	≥ 18y SAH	12m-mRS (0-3 vs. 4-6)	Hard	Pre-op	Age	HH	APACHE-II	Rebleed				

published models. By comparing these models, TAPS had a stable and good ability to predict 90-day outcomes in patients with aSAH in the three cohorts; moreover, we found that although these models targeted slightly different populations or outcome events, the variables included did not have more than six dimensions: (1) demographic information; (2) clinical status; (3) imaging information; (4) medical history; (5) laboratory tests; and (6) treatment modality. Notably, SAHIT showed better discrimination than TAPS in our validation and prospective cohorts. We acknowledge that SAHIT is an excellent prognostic model. However, its computational process is very complex, which may restrict its clinical application.

Interestingly, among these models, only TAPS emphasizes the importance of preoperative inflammatory biomarkers (collection time of NLR was not stated in Lai’s study), further illustrating the importance of the inflammatory response during EBI. Inflammation is an extremely broad category of physiological and pathophysiological host responses to infection and tissue injury [33]. aSAH has also been shown as a state of systemic inflammation and immunosuppression [34]. More attention has been paid to the relationship between inflammation and DCI after aSAH. For example, previous studies showed that WBC could predict DCI after aSAH, which may be the main reason for unfavorable outcomes [35–39]. DCI was a major risk factor for poor outcomes in aSAH patients treated with SC and EC in our previous study published using the LongTEAM database [40]. Therefore, we hypothesized that WBC mediated this process. However, whether other mechanisms could explain the poor prognosis due to WBC needs to be confirmed in further studies.

In the TAPS, predictors such as age, the WFNS grade, and the mFS grade have all been demonstrated in previous literature to be related to poor prognosis in patients with aSAH [41, 42]. The International Subarachnoid Aneurysm Trial (ISAT) in 2002 and the Barrow Ruptured Aneurysm Trial (BRAT) in 2012 indicated that endovascular coiling was superior to surgical clipping [43, 44]. In our previous study, EC shows advantages in discharge and 90-day outcomes, in-hospital complications, and the number of risk

factors over SC [40]. One study in 2018 regarded IVH as a binary variable in a multivariate regression model, and it was found to be associated with in-hospital mortality [45]. The potential reason for unfavorable outcomes caused by IVH might be the higher incidence of hydrocephalus and DCI [46]. In the TAPS, we used Graeb score to evaluate IVH more precisely, and it might be more helpful to improve the sensitivity to predict adverse events by incorporating Graeb score with mFS score. One study in 2018 conveyed the similar view, which showed accounting for IVH volume improved the prediction of DCI by the mFS [47].

The current understanding of EBI indicators is still limited, but it is encouraging that many reports have recently been published from basic research, which hypothesized from multiple aspects and designed experiments to successfully achieve the purpose of reducing specific EBI indicators [48–51]. In addition, in the field of clinical research, some articles have correlated certain preoperative parameters with prognosis using risk factor analysis to obtain indicators that have predictive value, such as reduced sulcal volume, higher serum levels of lactate dehydrogenase, monocyte-based inflammatory indices, glycemic indices, and high angiotensin-1 levels [52–56]. However, how to apply EBI indicators with predictive significance that were derived from basic research widely and quickly to clinical practice and, in turn, how to return EBI indicators with a predictive value that were derived from clinical research to basic research for mechanistic elaboration involve the development of translational medicine and are a complex process.

### Limitations

Some limitations of our study need to be discussed. First, the predictive model requires further external validation in a larger multicenter study. Second, when comparing different models, the results cannot deny the contribution of the original study because the different models target slightly different populations and outcome events. Third, the EBI indicators we included are all commonly used and easily accessible



in clinical practice, and some other EBI indicators from the basic research may improve the model's discrimination.

## Conclusions

In this study, we established a new 90-day predictive model named "TAPS" based on EBI indicators for aSAH patients, which contains six predictors (age > 55 years old, WFNS grade 4–5, mFS grade 3–4, Graeb score 5–12, WBC count >  $11.28 \times 10^9/L$ , and surgical clipping) with a total score of 7 points. TAPS is an efficient and easily handled model with good discrimination and calibration, which is helpful for neurosurgeons to quickly identify those patients who are likely to have unfavorable outcomes.

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**Author Contribution** Runting Li: conceptualization (equal); data curation (lead); formal analysis (lead); investigation (lead); methodology (equal); project administration (equal); software (lead); validation (lead); visualization (lead); writing original draft (lead); and writing review and editing (equal). Fa Lin: data curation (equal); methodology (equal); and software (equal). Yu Chen: data curation (equal); methodology (equal); and software (equal). Junlin Lu: data curation (equal); methodology (equal); and software (equal). Heze Han: data curation (equal); methodology (equal); and software (equal). Li Ma: data curation (equal). Yahui Zhao: data curation (equal). Debin Yan: data curation (equal). Ruinan Li: data curation (equal). Jun Yang: data curation (equal). Shihao He: data curation (equal). Zhipeng Li: data curation (equal). Haibin Zhang: data curation (equal). Kexin Yuan: data curation (equal). Ke Wang: data curation (equal). Qiang Hao: data curation (equal) and supervision (equal). Xun Ye: data curation (equal) and supervision (equal). Hao Wang: data curation (equal) and supervision (equal). Hongliang Li: data curation (equal) and supervision (equal). Linlin Zhang: data curation (equal) and supervision (equal). Guangzhi Shi: data curation (equal) and supervision (equal). Jianxin Zhou: data curation (equal) and supervision (equal). Yang Zhao: data curation (equal); resources (equal); and supervision (equal). Yukun Zhang: data curation (equal); resources (equal); and supervision (equal). Youxiang Li: data curation (equal); resources (equal); and supervision (equal). Shuo Wang: conceptualization (equal); funding acquisition (equal); resources (equal); supervision (equal); and writing review and editing (equal). Xiaolin Chen: conceptualization (equal); funding acquisition (equal); resources (equal); supervision (equal); and writing review and editing (equal). Yuanli Zhao: conceptualization (equal); resources (equal); supervision (equal); and writing review and editing (equal).

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

## Declarations

**Ethics Approval and Consent to Participate** This study was approved by the Institutional Review Board of the Beijing Tiantan Hospital (KY 2021–008-01). Informed consent was obtained from all individual participants or their authorized representatives included in the study. All the analyses were performed in accordance with the Declaration of Helsinki and the local ethics policies.

**Conflict of Interest** The authors declare no competing interests.

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