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Prognosis Predicting Score for Endovascular Treatment of Aneurysmal Subarachnoid Hemorrhage

A Risk Modeling Study for Individual Elderly Patients

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Abstract: The elderly patients with aneurysmal subarachnoid hemorrhage (aSAH) have a greater risk of poor clinical outcome after endovascular treatment (EVT) than younger patients do. Hence, it is necessary to explore which factors are associated with poor outcome and develop a predictive score specifically for elderly patients with aSAH receiving EVT.

The aim of this study was to develop and validate a predictive score for 1-year outcomes in individual elderly patients with aSAH underwent EVT.

In this 10-year prospective study, 520 consecutive aSAH elderly (age ≥ 60 years) patients underwent EVT in a single center were included. The risk factors, periprocedural, and 1-year follow-up data of all patients were entered in a specific prospective database.

The modified Rankin scale was used for evaluating clinical outcome. To optimize the model's predictive capacity, the original matrix was randomly divided in 2 submatrices (learning and testing). The predictive score was developed using Arabic numerals for all variables based on the variable coefficients (β) of multivariable logistic regression analysis in the learning set and the predictive performance evaluation was assessed in the testing set. The risk classes were constructed using classification criteria based on sensitivity and specificity.

The poor outcome rate at 1 year was 26.15%. Six risk factors, including age, hypertension, Hunt–Hess scale, Fisher scale, aneurysm location, and periprocedural complications, were independently associated with poor outcome and assembled the Changhai score. The discriminative power analysis with the area under the receiver operating characteristic curve (AUC) of the Changhai score was statistically significant (0.864, 0.824–0.904, $P < 0.001$). The sensitivity and specificity of the Changhai score were 82.07% and 78.06%, respectively.

Our study indicated that age, hypertension, Hunt–Hess scale, Fisher scale, aneurysm location, and periprocedural complications were independent risk factors of poor outcome for elderly aSAH patients underwent EVT. In combination with these risk factors, the Changhai score can be a useful tool in the prediction of clinical outcome but needs to be validated in various centers before it can be recommended for application.

(*Medicine* 95(7):e2686)

Abbreviations: 3 dimensional-DSA = 3D-digital subtraction angiography, ACA = anterior cerebral artery, Acoma = anterior communicating artery, aSAH = aneurysmal subarachnoid hemorrhage, BA = basilar artery, EVT = endovascular treatment, ICA = internal carotid artery, MCA = middle cerebral artery, mRS = modified Rankin scale, NST = neurosurgical treatment, PCA = posterior cerebral artery, Pcoma = posterior communicating artery, VA = vertebral artery.

INTRODUCTION

The incidence of aneurysmal subarachnoid hemorrhage (aSAH) increases with advancing age.[1–4] Hence, the elderly account for a significant number of the patients presenting with aSAH. Moreover, the elderly patients with aSAH have a greater risk of complications and poor outcomes than younger patients do, due to worse clinical status on admission, less active management, and a higher frequency of comorbidity.[5,6] Until now, the management of elderly patients with aSAH is still a clinical challenge.

With the prospect of reducing the risk of rebleeding without the need for craniotomy, thus reducing surgical trauma, endovascular treatment (EVT) was conceived as a promising alternative to neurosurgical treatment (NST), especially in elderly and poor-grade patients with aSAH.[7] The keynotes of EVT for elderly patients with aSAH were reducing complication rate, improving safety and prognosis. However, the safety and effectiveness of EVT for elderly aSAH patients were affected by a great many factors, including patient conditions, lesion characteristics, and procedure-related factors. There were some previous studies reporting that the risk factors of outcomes and complications of aSAH patients underwent EVT.[8,9] However, they either lacked comprehensive factors included or age stratification, which made them difficult to evaluate the risk of EVT for elderly aSAH patients comprehensively.[7,10,11] Hence, it is necessary to explore which factors are associated with poor outcome and develop a risk score specifically for elderly patients with aSAH receiving EVT that can be easily used in clinical practice and facilitate clinical decision-making process.

Accordingly, our aim of the present work is to evaluate the outcome of aSAH in elderly patients underwent EVT, explore preliminarily risk factors, and then establish a mathematical predicting model for poor outcome after EVT for elderly patients with aSAH.

MATERIALS AND METHODS

Patient Selection

In this prospective study, consecutive elderly aSAH patients underwent EVT over a period of 10 years (June 2004–June 2014) in our center were included. Patients inclusion criteria were age $\geq$ 60 years; and with aSAH treated endovascularly. Patients with any of the following were excluded: specific types of aneurysms such as traumatic aneurysm, pseudoaneurysm, and iatrogenic aneurysm; and patients with incomplete medical records. The Ethics Committee of Changhai hospital approved the study and informed consent was obtained from all patients before any procedure. Figure 1 shows a flow diagram of the whole population of elderly patients with aSAH treated at our institute during the study period.

Definitions of Variables and Data Collection

The research team entered the risk factors, intraoperative and 1-year follow-up data in a specific prospective database. All the selected predictive factors of poor clinical outcome including patient-related, lesion-related, and procedure-related variables were analyzed blind to outcome events. Particularly, clinical grade including Fisher scale[12] and Hunt–Hess scale[13] were evaluated preprocedure by operators. Lesion-related variables were defined and calculated based on the 3-dimensional digital subtraction angiography image according to Dhar et al's[14] and Bor et al's[15] studies. Aneurysms located on internal carotid artery (ICA), posterior communicating artery (Pcoma), vertebral artery (VA), and basilar artery (BA) were divided into the group of located proximal the circle of Willis. Others including middle cerebral artery (MCA), anterior cerebral artery (ACA), anterior communicating artery (Acoma), posterior cerebral artery (PCA), and BA apex were divided into the group of located on and distal

FIGURE 1. Procedure flow diagram of elderly patients with aSAH underwent EVT procedure at our institute. aSAH = aneurysmal subarachnoid hemorrhage, EVT = endovascular treatment.

the circle of Willis. Wide-necked aneurysms were defined as having a large aneurysm neck (>4 mm) and/or a small dome-to-neck ratio ($\leq$2). The aortic arch was classified according to the origin of the arch vessels.[16] We divided the aneurysms size into 4 subgroups (<3, 3–6, 7–10, and >10 mm). EVT strategies were classified into coiling only group, double catheter-assisted group, stent-assisted group, and balloon-assisted group.

Procedure Technique

For aSAH patients, the treatment strategies (clipping or EVT) were jointed discussion and development by neurosurgeons and endovascular neurosurgeons. Meanwhile, if EVT was decided, the EVT strategies were decided by endovascular neurosurgeons based on the morphology of aneurysm and parent vessels. In this study, 5 well-trained and experienced endovascular neurosurgeons treated these patients. All procedures were performed under general anesthesia using a transfemoral approach and systemic heparinization aiming for elevation of the activated clotting time to a level of 2 to 3 over baseline. A loading dose of clopidogrel and aspirin (300 mg each) was administered orally or rectally before the procedure if a stent was necessary.

A 6 French guiding catheter was inserted into the distal ICA or vertebral artery as appropriate. All microcatheters, coils, and stents (if needed) were delivered through this catheter. If acute thrombosis occurred during the procedure, Tirofiban, a glycoprotein IIb/IIIa inhibitor was used. The immediate angiographic results were evaluated independently by 2 endovascular neurosurgeons using Raymond classification.[17]

Follow-Up Protocol and Outcome

The main outcome measure was modified Rankin scale (mRS).[18] The poor outcome was defined as mRS $\geq$ 3. The periprocedural complications included hemorrhagic and ischemic stroke, pulmonary infection, acute heart failure, and acute renal dysfunction, hemorrhage of digestive tract which requiring blood transfusion occurred after EVT. Hemorrhagic stroke included intraprocedural rupture and rebleeding after EVT. Intraprocedural rupture was defined as the extravasation of contrast material demonstrated on concurrent angiography, regardless of the extrusion of coil, microcatheter, or microguidewire outside the lumen of an aneurysm. Rebleeding including recurrent SAH, subdural hemorrhage, and intraparenchymal hemorrhage were diagnosed according to a new clinically neurological defect and confirmed on computed tomographic (CT)/magnetic resonance (MR) imaging within 30 days after EVT. Ischemic stroke including thromboembolic events and vasospasm-related ischemic events were defined as a vessel occlusion recognized by angiography at the period of EVT, or a clinically evident ischemic stroke with evidence of infarction on diffusion-weighted imaging, which occurred within 30 days after EVT.

All patients underwent independent neurological evaluation before the procedure, discharge, 30 days, and 1 year after the procedure. All patients underwent a cerebral CT scan before procedure and immediately after procedure. Whereas additional CT/MR scan was performed in patients with suspected neurological complications.

Statistical Analyses

These data were expressed as mean and standard deviations (mean ± SD) or as absolute frequencies and percentages. $P < 0.05$ (2-tailed) was considered statistically significant. All
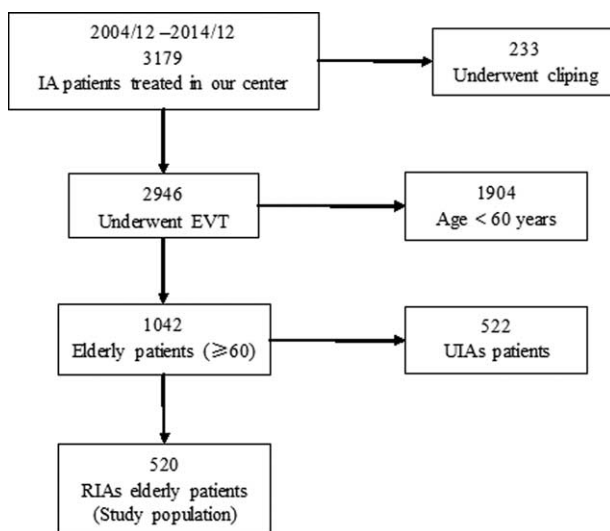
statistical analyses were performed by using the SPSS v.19 for Windows statistical software package (SPSS Inc., Chicago, IL, USA).

To optimize the model's predictive capacity, the original matrix was randomly divided in 2 submatrices (learning and testing) and all the candidate variables were arranged in a dichotomous way. The model parameters were estimated in the learning set and the predictive performance evaluation was assessed in the testing set.

In learning set, univariable analysis by *t* tests, nonparametric tests, χ^2 tests or Fisher exact tests depending on the distribution of the variables were used to determine which variables would be included in the initial multivariable logistic regressions. If the *P* value of the univariable model was <0.1, then it was considered for inclusion in the multivariable model and the other variables were set aside.

The first round multivariables logistic regression with stepwise backward maximum likelihood ratio method were used for the variables to be included. If continuous variable existed in the model of first round regression, then this variable was transform into category variable. And then the enter method logistic regressions were used for the variables which significant in first round logistic regressions after transforming. The beta coefficients of significant variables in second round logistic regressions were used to form the risk score by |bete| of variable/minimal |bete| after quantizing and the risk classes were constructed using classification criteria based on sensitivity and specificity.[19] The discriminative ability was analyzed with the area under the receiver operating characteristic curve (AUC) and the Hosmer–Lemeshow goodness-of-fit test was used to determine calibration of the model (low *P* values indicate poor goodness-of-fit).

The score model was validated in testing set. In testing set, the risk score model was used to assign a score for every patient. Then, the discriminative ability, sensitivity, and specificity of risk score were analyzed in testing set and compared with learning set.

RESULTS

Clinical Outcomes

Five hundred twenty elderly patients received EVT procedures and completed follow-up at 1 year after procedures during the study period. Periprocedural complications occurred in 150 patients (28.85%, 150 of 520). Fifty-six of these (10.77%, 56 of 520) resulted in death. Poor outcome (mRS $\geq$ 3) occurred in 136 patients (26.15%, 136 of 520). Specially, during the period of study, there were 41 patients with symptomatic cerebral vasospasm refractory to hypertensive therapy. All of them accepted endovascular procedures again, including balloon angioplasty in 3 cases and intra-arterial infusion of Fasudil hydrochloride in 38 cases. The rates of mortality, complications, and poor outcome were compared within 2 sets. The results show that there are no statistical differences between these 2 sets. The detailed results were provided in Table 1.

Univariate Analysis of Outcomes

As results of univariable analysis, the *P* values of age, hypertension, coronary heart disease, chronic obstructive pulmonary disease, Hunt–Hess scale, Fisher scale, aneurysm located on and distal the circle of Willis, wide-necked aneurysm, with bleb on aneurysm sac, irregular aneurysm shape, EVT strategies, timing of EVT, and periprocedural complications were <0.1. The results were shown in Table 2. Therefore, these factors were considered for inclusion in the multivariable analysis.

Multivariate logistic regression followed by backward stepwise analysis determined that only age, hypertension, Hunt–Hess scale, Fisher scale, aneurysm located on and distally to the circle of Willis, and periprocedural complications were independently associated with poor outcome. Further, the age was divided into 2 subcategory ($\geq$75 years or not) and second round multivariate logistic regression analysis followed by enter method was performed. The results were shown in Table 3.

Score Model Development

Six risk factors including age $\geq$ 75 years, hypertension, Hunt–Hess scale, Fisher scale, aneurysm located on and distally to the circle of Willis, and periprocedural complications were used to form the risk score by |bete| of variable/minimal |bete|. The model named Changhai score and shown in Table 4. The discriminative power analysis with the AUC of the Changhai score was statistically significant (0.864, 0.824–0.904, *P* < 0.001). The calibration of the Changhai score was determined significantly higher (*P* = 0.258) with the Hosmer–Lemeshow goodness-of-fit test. The sensitivity and specificity of the Changhai score were 82.07% and 78.06%, respectively.

TABLE 1. Periprocedural Complications and 1-y Outcome of 520 Patients

	Total Sets (%), n = 520	Learning Sets (%), n = 416	Testing Sets (%), n = 104	*P*
Periprocedural complications	150 (28.85)	116 (27.88)	34 (32.69)	0.333
Intraprocedural rupture	12 (2.31)	9 (2.16)	3 (2.88)	0.942
Ischemic stroke	36 (6.92)	30 (7.21)	6 (5.77)	0.604
Rebleeding	22 (3.27)	16 (2.88)	6 (4.81)	0.684
Pulmonary infection	62 (11.92)	47 (11.30)	15 (14.42)	0.379
Acute heart failure	7 (1.35)	5 (1.20)	2 (1.92)	0.924
Acute renal dysfunction	6 (1.15)	5 (1.20)	1 (0.96)	1.000
Hemorrhage of digestive tract	5 (1.35)	4 (0.96)	1 (0.96)	1.000
Death	56 (10.77)	43 (10.34)	13 (12.50)	0.546
Poor outcome (mRS $\geq$ 3)	136 (26.15)	106 (25.48)	30 (28.85)	0.485

Periprocedural complications included 7 adverse events occurred within 30 d after procedure. The mortality rate and poor outcome rate were assessed 1 y after procedure.

mRS = modified Rankin scale.

TABLE 2. Clinical, Lesion, Procedural Characteristics, and Periprocedural Complications Related to Poor Outcome in Learning Sets (416 Patients)

	Poor Outcome		
Variables	**No**	**Yes**	**P**
Patient-related factor			
Age, y (mean = 67.88 ± 6.44), mean ± SD	67.69 ± 6.39	69.12 ± 6.48	0.034
Age, y			
60−74	258	79	0.049
≥75	52	27	
Gender			
Male	92	36	0.409
Female	218	70	
Smoking			
No	291	97	0.402
Yes	19	9	
Hypertension			
No	131	28	0.004
Yes	179	78	
Coronary heart disease			
No	281	87	0.017
Yes	29	19	
Renal function insufficiency			
No	306	104	1.000
Yes	4	2	
Chronic obstructive pulmonary disease			
No	293	90	0.002
Yes	17	16	
Diabetes mellitus			
No	281	92	0.261
Yes	29	14	
Long-term use of antiplatelet drug			
No	301	102	0.903
Yes	9	4	
With other cerebrovascular diseases			
No	267	91	1.000
Yes	43	15	
Fisher scale			
1−2	263	34	0.000
3−4	47	72	
Hunt−Hess scale			
1−3	295	79	0.000
4−5	15	27	
Lesion-related factors			
Location I			
Anterior circulation	293	96	0.154
Posterior circulation	17	10	
Location II (the Circle of Willis)			
On and distal	187	47	0.004
Proximal	123	59	
Multiple aneurysms			
Single	235	81	0.899
Multiple	75	25	
Maximum dimension, mm			
Tiny (<3)	27	9	0.833
Small (3−6)	51	21	
Medium (7−10)	196	66	
Large (>10)	36	10	
Wide-necked aneurysms			
No	193	61	0.391
Yes	117	45	

TABLE 2. (*Continued*)

	Poor Outcome		
Variables	No	Yes	*P*
Proximal parent artery stenosis			
No	303	102	0.625
Yes	7	4	
With bleb			
No	255	76	0.020
Yes	55	30	
Aneurysm shape			
Regular	240	70	0.020
Irregular	70	36	
Type of aortic arch			
I	305	102	0.410
II	4	3	
III	1	1	
Parent artery configuration			
Side wall	67	23	0.985
Bifurcation	243	83	
Procedure-related factors			
Intervention strategy			
Coiling only	181	65	0.773
Double catheter-assisted	23	7	
Stent-assisted	92	28	
Balloon-assisted	14	6	
Immediate embolization result			
I	117	42	0.589
II	80	31	
III	113	33	
Timing of coiling after rupture, h			
<72	205	81	0.049
≥72	105	25	
Periprocedural complications			
No	292	70	0.000
Yes	18	36	

SD = standard deviation.

In order to make the Changhai score become a handy tool, we divide this continuous score into 3 subgroups, indicating the EVT procedure could be predicted as being a low risk (rate 6.44%), a moderate risk (rate 41.10%), or a high risk (rate 83.33%) for poor outcome. The results were shown in Table 5.

Score Model Validation

In testing set, the AUC of the Changhai score was statistically significant (0.891, 0.825–0.956, $P < 0.001$). The calibration of the Changhai score was statistically significant ($P = 0.273$). The sensitivity and specificity of the Changhai score were 90.00% and 83.78%, respectively. All of these 4 parameters were slightly higher than in learning set.

Comparisons of the Changhai Score With Its Components

In learning set, comparisons of the receiver operating characteristic curve (ROC) AUCs showed that the Changhai score was superior to the ROC AUCs of these 6 factors including age, hypertension, Hunt–Hess scale, Fisher scale, aneurysm located on and distally to the circle of Willis, and periprocedural complications for predicting 1-year outcome. The results were shown in Figure 2.

DISCUSSION

The findings we present are based on a prospective real-world cohort study comprising 520 consecutive elderly aSAH patients hospitalized for EVT in a single center. In this study, we developed and validated a prognosis predictive score (Changhai score) to predict 1-year clinical outcome for individual elderly patients with aSAH underwent EVT. In Changhai score, 6 factors including age, hypertension, Hunt–Hess scale, Fisher scale, aneurysm located on and distally to the circle of Willis, and periprocedural complications were included. The discriminative power and calibration of the Changhai score were significantly higher.

Along with the development of neuro-interventional techniques and materials, EVT has become an important method for treatment of intracranial aneurysms.[20,21] The choice of treatment between EVT and surgical clipping for an individual elderly patient with aSAH remains a controversial issue. Even if some studies have shown that EVT is safer than surgical clipping in these patients, there is still lacking of randomized, clinical trial to support it.[7,22] Poor prognosis after aSAH is always associated with age, especially for elderly patients with a high incidence of adverse outcomes.[18,23,24] The rate of poor outcome and mortality at 1 year in our cohort was lower than the results reported in other previous studies.[7,22,25] It may be

TABLE 3. Multivariate Logistic Regression Analysis of Significant Variables Related to Poor Outcome 1-y After Coiling

Variables	β	SE	Wals	*P*	OR	95% CI
Age $\geq$ 75 y	0.511	0.170	8.969	0.003	1.666	1.193–2.327
Hypertension	0.249	0.153	2.649	0.104	1.283	0.950–1.733
Hunt–Hess score 4–5	0.564	0.224	6.329	0.012	1.758	1.133–2.729
Fisher score 3–4	1.172	0.146	64.825	0.000	3.229	2.427–4.295
Located on and distal the Circle of Willis	0.347	0.144	5.829	0.016	1.415	1.067–1.874
Periprocedural complications	0.846	0.198	18.248	0.000	2.330	1.580–3.434
Constant	0.408	0.284	2.061	0.151	1.504	

CI = confidence interval, OR = odds ratio.

because that the cut-off age for elderly patients in our study was 60 years old and younger than these previous studies. After classification of age, our results shown 75 years old is a critical age which affecting outcome for elderly aSAH patients underwent EVT. This is similar to some previous studies.[24–26]

In aneurysmal SAH, the neurological condition of patient on admission and the amount of extravasated blood seen on CT scan are most closely related to outcome.[5,6,11,25] However, the contribution made by each specific predictor remains unknown for elderly aSAH patients. Not surprisingly, Fisher grade has the most profound influence on 1-year poor outcomes, followed by periprocedural complications and Hunt–Hess grade.[18,27,28] Although, EVT possess many advantages included minimally invasive and have become an important method for aSAH patients, elderly patients frequently present higher periprocedural complications.[24,29] The reasons were that elderly patients generally have tortuous vascular path and worse condition of parent artery due to atherosclerotic stenosis and then prolonged procedural time. In our study, periprocedural complications rate was higher than the rates reported in previous studies without focusing on elderly patients only.[11,27,30] Although, we have not analyzed the relation between other factors and periprocedural complications, aneurysm located on and distal the circle of Willis was an independent risk factors of poor outcome, which may be due to relatively smaller diameter of parent artery, longer procedure vascular path, and lead to higher

complications rate. What is interesting is that some factors which previously been consider as risk factors included intervention strategies, treatment opportunity, and immediate embolization result were proved have nothing to do with poor clinical outcome.

Some studies have proved that blood pressure of patients in acute phase of hemorrhagic stroke may affect outcome of patients.[31] However, blood pressures of SAH patients were fluctuant and controllable. After aneurysm ruptured, increasing of blood pressure may be a response performance of intracranial hypertension. Previously study has indicated that intracranial pressure elevation was independent risk factors of cerebral infarction after aSAH.[32] When established the protocol of this study, we just included history of hypertension as a potential risk factor instead of blood pressure after onset. Regarding the patient's clinical conditions, in our model, history of hypertension was found to be slightly predictive of poor outcome. This may be due to elderly patients with history of hypertension frequently accompanying more systemic disease. Meanwhile, for elderly patients with aSAH, blood pressure adjustment and managing were difficult. Hence, for elderly aSAH patients, blood pressure must be controlled to maintenance of the relationship between cerebral perfusion pressures and the risk of ischemic stroke and rebleeding during the whole period of treatment.[33]

Timing of EVT is critical for rupture aneurysm. Delayed EVT may increase the risk of rebleeding or vasospasm. However, it has not confirmed the effect of timing on clinical outcome. Our results shown that the timing of EVT was not an independently factor associated with poor outcome. Moreover, coronary heart disease and chronic obstructive pulmonary disease were proved been related to 1-year poor outcome with univariate analysis. However, these 2 factors did not included in multivariables logistic model. The reason may be that coronary heart disease and chronic obstructive pulmonary disease were closely related to periprocedural complications and affected by

TABLE 4. Changhai Score model of Poor Outcome

Risk Factors	Score
Age, y	
$\geq$75	2
<75	0
Hypertension	1
Hunt–Hess score	
1–3	0
4 or 5	2
Fisher scale	
1 or 2	0
3 or 4	5
Aneurysm location	
Located on and distal the Circle of Willis	0
Located proximal the Circle of Willis	1
Periprocedural complications	3
Total score	16

TABLE 5. Predicted Poor Outcome Rate in 3 Categories of Changhai Score

Score Classification	Total Score	Poor Outcome Rate, %	Risk Classification
I	0–3	7.28	Low
II	4–7	45.71	Moderate
III	8–16	78.00	High
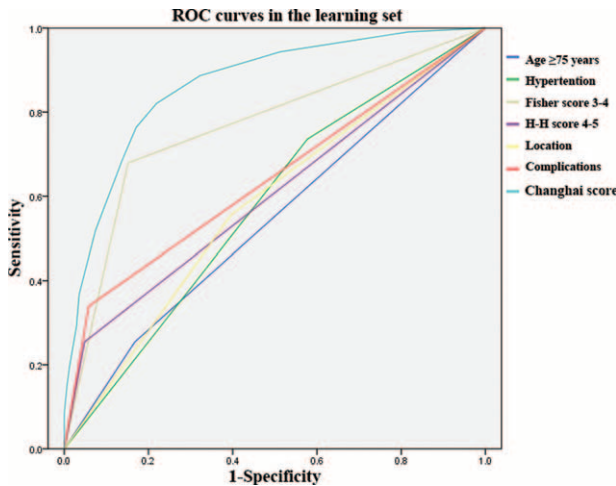
FIGURE 2. Comparisons of the Changhai score with its components according to the ROC AUC to predict 1-y outcome. AUC = area under the receiver operating characteristic curve, ROC = receiver operating characteristic curve.

the linear relationship between them and might explain the interaction between coronary heart disease, chronic obstructive pulmonary disease, and periprocedural complications.

In this Changhai score, 6 factors were included. All of them were independent risk factors of poor outcome and can be as predictive factors for outcome. In order to embody the advantages of our new score model, we compared Changhai score with its component variables and the results shown that the ROC AUC of Changhai score was superior to age, hypertension, Hunt–Hess scale, Fisher scale, aneurysm located on and distally to the circle of Willis, and periprocedural complications for predicting 1-year outcome. That suggests that the Changhai score is better for predicting outcome of elderly patients with aSAH underwent EVT.

There are some limitations in the present study. First, our study was conducted in a single center and suffered from the limitations that are inherent in this kind of study. Prospective validation studies should be conducted in multi-center trial with larger sample size to confirm our findings. Although this study involved 520 elderly patients, it did not assess all the variables that may have influenced outcome because the analysis lacked the statistical power to adequately identify the relative importance of several other variables occurring at a low frequency in the study group. Moreover, the assessment of some anatomic characteristics was subjective and strictly related to the definitions utilized.

CONCLUSIONS

Our study indicated that age, hypertension, Hunt–Hess scale, Fisher scale, aneurysm located on and distally to the circle of Willis, and periprocedural complications were independent risk factors of poor outcome for elderly aSAH patients underwent EVT. In combination with these risk factors, the Changhai score can be a useful tool in the prediction of outcome but needs to be validated in various centers before it can be recommended for application.

ACKNOWLEDGMENTS

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