

Early-stage serum Stanniocalcin 1 as a predictor of outcome in patients with aneurysmal subarachnoid hemorrhage

Qin Jun, MD^{a,*} , Weijian Luo, MD^b

Abstract

Stanniocalcin-1 (STC1) takes part in anti-inflammatory and anti-oxidative processes, thus demonstrating neuroprotective properties. Early brain injuries associated with initial subarachnoid hemorrhage typically led to secondary cerebral infarction and poor outcomes. This retrospective study aimed to clarify the clinical significance of serum STC1 level in patients with subarachnoid hemorrhage.

We collected demographic information, comorbidities, neurological status in detail. All blood samples were collected on admission. Enzyme-linked immunosorbent assay kits were used to detect the serum level of STC1. Spearman analysis was used to explore the relationship between STC1 and clinical severity. Multivariate logistic regression was used to investigate the prognostic role of STC1 in patients with aneurysmal subarachnoid hemorrhage (aSAH). Receiver operating characteristic curve was performed to investigate the power of STC1 in predicting outcome in aSAH patients.

Serum STC1 concentration was significantly higher in aSAH patients than in healthy individuals. Serum concentration of STC1 positively correlated with Hunt-Hess grade ($r=0.62, P<.01$) and Fisher grade ($r=0.48, P<.01$), and negatively correlated with Glasgow Coma Scale on admission ($r=-0.45, P<.01$). Patients with delayed cerebral ischemia (DCI) had higher level of serum STC1 than those without DCI (13.12 ± 1.44 vs $8.56 \pm 0.31, P<.01$). Moreover, patients with poor outcome had higher concentration of STC1 than patients with good outcome (11.82 ± 0.62 vs $8.21 \pm 0.35, P<0.01$). Results of univariate and multivariate logistic analysis revealed that Hunt-hess III–IV, DCI, and high STC1 level were independent risk factors associated with poor outcome of patients with aSAH. Further analysis revealed that combination of STC1 with Hunt-hess grade was more superior to 2 indicators alone in predicting clinical outcome of aSAH patients.

STC1 can be used as a novel biomarker in predicting outcome of patients with aSAH, especially when combined with Hunt-hess grade.

Abbreviations: aSAH = aneurysmal subarachnoid hemorrhage, CRP = C-reactive protein, DCI = delayed cerebral ischemia, GCS = Glasgow Coma scale, GOS = Glasgow Outcome Scale, ROC = receiver operating characteristic, STC1 = Stanniocalcin-1, WFNS = World Federation of Neurosurgical Societies.

Keywords: Biomarker, delay cerebral ischemia, prognosis, Stanniocalcin 1, subarachnoid hemorrhage

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This study was approved by the Ethics Committee of the Fourth Affiliated Hospital of Guangxi Medical University and informed consent of every patients included was signed by their relatives.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) was caused by rupture of intracranial aneurysms and it had high mortality rate and disability rate. Previous studies revealed that the average case fatality rate of aSAH was 27% to 44% in China.^[1] A hospital-based prospective multicenter study showed that the cumulative mortality rate of aSAH patients at 1, 3, 6, and 12 months after aSAH onset was 16.9%, 21.2%, 23.6%, and 24.6%, respectively.^[2] Therefore, it is particularly important to assess the severity of patient's condition at early stage. This enables clinicians to screen out patients at high risk and to provide effective early interventions. Many studies have found that many risk factors were closely related to the clinical outcome of aSAH patients. Several risk factors, such as age, WFNS (World Federation of Neurosurgical Societies) score, Hunt-hess score, Fisher grade, and postoperative complications, were significantly associated with clinical outcome of subarachnoid hemorrhage patients.^[3–5] Besides, many molecules were involved in the pathological process after aSAH and some of them played crucial roles in causing neurological complications. Previous studies have found that biochemical markers have a high accuracy in predicting the clinical prognosis of patients with aSAH.^[6,7] However, there are still many deficiencies in predicting the complications and clinical

prognosis of patients with aSAH. The overall accuracy of treating neurologists in predicting outcome ranged from 78% to 88%, while it was not reliable for biomarkers in predicting prognosis of aSAH solely based on the performance of imaging or clinical physicians.^[8] In recent years, clinical prediction models that combined biomarkers and severity have emerged, while the predictive value of clinical prediction models differed among studies.

Stanniocalcin-1 (STC1) is a 25-kD homodimeric glycoprotein hormone involved in calcium regulation in bony fish, where elevation of serum calcium triggers the release of STC1 from the corpuscles of Stannius, organs associated with the kidneys. It is expressed in multiple normal organs such as the skin, lung, ovary, cervix, and thymus. It was reported that STC1 carries out autocrine and paracrine regulatory functions with pleiotropic rather than classical endocrine hormonal effects. These functions may include cell proliferation and differentiation, migration, survival or apoptosis, vascular remodeling.^[9,10] Therefore, they have received interest as a promising candidate for several potential clinical applications and several studies have demonstrated that STC1 exhibit this potential role as a prognostic biomarker, as well as tracking progression of disease.^[11,12]

Because of the hypoxia condition and accumulation of metabolites postsubarachnoid hemorrhage, patients would unavoidably suffer early brain damage. More and more studies have found that the extent of early brain damage was closely associated with complications and was the primary cause of high mortality and morbidity. It was found that STC1 expression increased under hypoxic conditions and hypoxia-induced STC1 expression could inhibit cell apoptosis. Therefore, these gave us a hint that STC1 might be important molecular factor that mediated the progression of aSAH. In this study, we found that serum STC1 was significantly associated with clinical severity of aSAH. STC1 was elevated in patients with delayed cerebral ischemia (DCI) and poor outcome. Further analysis also revealed that serum STC1 was an independent risk factor of poor outcome of aSAH patients. Moreover, receiver operating characteristic (ROC) revealed that serum STC1 was a novel, complementary biomarker in predicting outcome of patients with aSAH.

2. Methods

2.1. Patients

We performed this study in the Department of Critical Care Medicine and Neurosurgery in the Fourth Affiliated Hospital of Guangxi Medical University during October 1, 2015 to May 30, 2019. Patients who were included were all diagnosed by head computed tomography (CT) and head CT angiography or digital subtraction angiography. Patients who reached hospital more than 72 hours after their symptom onset were excluded. Besides, we also exclude patients who were accompanied by intracerebral arteriovenous malformations, moyamoya disease. All patients were treated with therapeutic regimen and subsequently received neurosurgical clipping or coiling. The recruited healthy control population was recorded as the control group. This study was approved by the Ethics Committee of the Fourth Affiliated Hospital of Guangxi Medical University (Institutional Review Board number:2015008) and all the participating patients signed the informed consent form.

2.2. Clinical data collection and assessment

Demographic information (sex, gender) and comorbidities were recorded in detail. Neurological status was assessed by using Glasgow Coma scale (GCS) and Hunt-hess grade. Besides, the severity of aSAH was evaluated using Fisher grade according to the presentation on head CT on admission. We collected postoperative complications, such as DCI, rebleeding, hydrocephalus, epilepsy, and systematic infections. Patients who underwent surgical procedure would be routinely received a head CT on the first day after operation and at any time if patients suffered clinical deterioration. DCI was defined as a neurological deterioration (GCS dropped more than 2 points) or a new infarction on head CT after operation. Clinical outcome assessment was performed by using Glasgow outcome scale (GOS). Poor outcome was defined as GOS score 1 to 3 and good outcome was defined as GOS score 4 to 5 at 12 months.

2.3. Blood samples

All blood samples were collected on admission. Blood was centrifuged at 3000 rpm/min for 5 minutes at 4° C by using a refrigerated centrifuge after taking 2 mL of blood from the patients. Then we transferred the supernatant to a clean EP tube and stored them in a -80°C freezer. Enzyme-linked immunosorbent assay kits for detecting STC1 and C-reactive protein (CRP) in peripheral blood were purchased from USCN (Wuhan USCN business Co Ltd). All operations are performed according to the instructions.

2.4. Statistical analysis

Continuous variables are represented by mean±SD. Comparisons between the 2 groups were performed using independent sample *t* tests and one-way ANOVA analysis was used for 3 or more groups comparisons. Univariate and multivariate regression analyses were used to analyze prognostic-related independent risk factors. ROC curves were used to demonstrate the ability of different prognostic factors to predict poor prognosis. A *P* value of less than .05 was considered to be statistically different. All statistical analysis and graphics production were done with SPSS 21 and Graphpad 5.0.

3. Results

3.1. Baseline information of included patients

This retrospective study included 121 patients with aSAH. There were 69 males and 52 females and the average age of included patients was 56.68±10.03 years old. We routinely record patients' accompanied diseases and there were 41 patients with hypertension, 21 patients with diabetes, and 28 patients with current smoking. The neurological status score of aSAH at admission was mainly based on GCS and Hunt-hess grade. This study found that there were 31 patients with GCS score < 9, 42 patients with high Hunt-hess grade (III–IV). Details of baseline information was presented in Table 1. All control groups were from the annual check-up patients in the physical examination center. The age of the control group was between 18 and 65 years old, and the male to female ratio was 23:17. There were 16 patients with hypertension, 7 patients with diabetes, and 10 patients with current smoking.

Table 1
Baseline information of patients included.

Variables	N (%)
Male (%)	69 (57.02)
Age (yr)	56.68 ± 10.03
Hypertension	41 (33.88)
Diabetes	21 (17.36)
Alcohol consumption	35 (28.92)
Smoking	28 (23.14)
GCS	
3–8	31 (25.62)
9–12	50 (41.32)
13–15	40 (33.06)
Hunt-hess	
I–II	79 (65.29)
III–IV	42 (34.71)
Fisher	
I–II	49 (40.50)
III–IV	72 (59.50)
Intraventricular hemorrhage	21 (17.36)
Aneurysm locations	
Anterior circulation artery	104 (85.95)
Posterior circulation artery	22 (14.05)
Surgical approaches	
Clipping	94 (77.69)
Coiling	27 (22.31)
GCS= Glasgow coma scale	
CRP (mg/mL)	1.35 (1.01–1.21) 0.01 1.13 (0.83–1.14) 0.04

CRP = C-reactive protein, GCS = Glasgow coma scale, STC1 = Stanniocalcin 1.

3.2. Serum level of STC1 change after aSAH

Serum STC1 concentration was substantially higher in aSAH patients than in healthy individuals (Fig. 1A). Spearman correlation analysis revealed that serum level of STC1 was positively correlated with Hunt-hess grade ($r=0.62$, $P<.01$), Fisher grade ($r=0.48$, $P<.01$) (Fig. 1 D, C), but negatively correlated with GCS on admission ($r=-0.45$, $P<.01$) (Fig. 1B). CRP was an acute phase reaction protein of aSAH and it was an independent risk factor of poor outcome in aSAH. Further analysis found that serum level of STC1 correlated with serum level of CRP ($r=0.53$, $P<.01$) (Fig. 1E).

3.3. Association between serum STC1 and clinical outcome

Then DCI was a serious complication of aSAH. We found that patients with DCI had higher level of serum STC1 than those without DCI (13.12 ± 1.44 vs 8.56 ± 0.31 , $P<.01$) (Fig. 2A). Besides, we used GOS to assess the clinical outcome of aSAH in 1 year after surgery. Patients with poor outcome had higher concentration of STC1 than patients with good outcome (11.82 ± 0.62 vs 8.21 ± 0.35 , $P<.01$) (Fig. 2B).

3.4. Prognostic role of STC1 in aSAH patients

Next, we tried to find relationship between serum concentration of STC1 and prognosis of aSAH patients. We used univariate and multivariate analysis to analyze risk factors associated with poor outcome of patients with aSAH. The results showed that Hunt-hess III–IV, DCI, and high STC1 level were independent risk factors associated with poor outcome of patients with aSAH (Table 2). Furthermore, we found that STC1 was also an

independent risk factor associated with DCI (Table 3). These results indicated that STC1 might play crucial role in the progression of aSAH. Finally, we used ROC to investigate the role of STC1 in predicting poor outcome. The results showed that AUC of STC1 and Hunt-hess grade were 0.847 and 0.720, respectively. But when we combined those 2 indicators together, we found that the AUC was 0.910 in predicting poor outcome (Fig. 3).

4. Discussion

In this study, we found that serum level of STC1 positively correlated with Hunt-hess grade and Fisher grade, while negatively correlated with GCS scores. Patients with DCI had higher serum level of STC1 than patients without DCI. Besides, STC1 was higher in patients with poor outcome than in patients with good outcome. Univariate and multivariate logistic regression analysis revealed that high serum STC1 was an independent risk factor of poor outcome and DCI in aSAH patients. Moreover, ability of combination of STC1 and Hunt-hess grade in predicting clinical outcome of aSAH patients was more superior to 2 indicators predicting alone. These results indicated that STC1 could be used as a novel and complementary in predicting outcome of patients with aSAH.

Several studies found STC1 was involved in neurological diseases, such as glioma and ischemia stroke. The previous study demonstrated that STC1 was obviously elevated in glioma cells and subsequently enhanced stem-like traits by regulating NOTCH signaling.^[15,16] Other studies revealed that STC1 might be a neuroprotectant in neurological diseases.^[17,18] Besides, by constructing mouse model, Durukan et al found STC1 was elevated under hypoxic condition and it was dispensable for functional recovery after ischemia stroke.^[8] Hypoxic condition can induce the expression of STC1 and high level of STC1 can enhance neuron resistance to hypoxia.^[19] It is well known that stroke can trigger hypoxia and inflammatory reactions, which are important pathological processes during secondary brain injury that may lead to poor outcome. These results indicated that STC1 might play a crucial role in regulation inflammation and hypoxic condition in cerebrovascular diseases. Therefore, it is reasonable to assume whether the expression of STC1 will change after stroke. In this study, we explored STC1 expression in peripheral blood for the first time. We found that STC1 was higher in patients with worse neurological status and poor outcome and identified it as a novel biomarker in patients with aSAH.

Neurological scales, such as GCS, Hunt-hess, and WFNS, are always widely used in clinically to evaluate the clinical severity or to predict clinical outcome of patients with aSAH. But the evaluation of clinical severity solely based on scales may be too rough and sometimes too subjective.^[20,21] Different doctors who evaluated the same patient at the same time may have different results. So in recent years, biochemical markers have received unprecedented attention. Numerous studies found that biochemical markers (CRP, S100 β , NSE, etc) could be used alone to assess the severity and predict poor outcome in patients with aSAH.^[22–24] Our results showed that AUC of STC1 was 0.847, which was acceptable in predicting outcome of aSAH patients.

But in this study, we have not used another validated cohort to confirm its predictive ability. If the heterogeneity between patients is taken into account, different results may be achieved. Therefore, a combined logistic model was necessary in predicting outcome of aSAH patients.

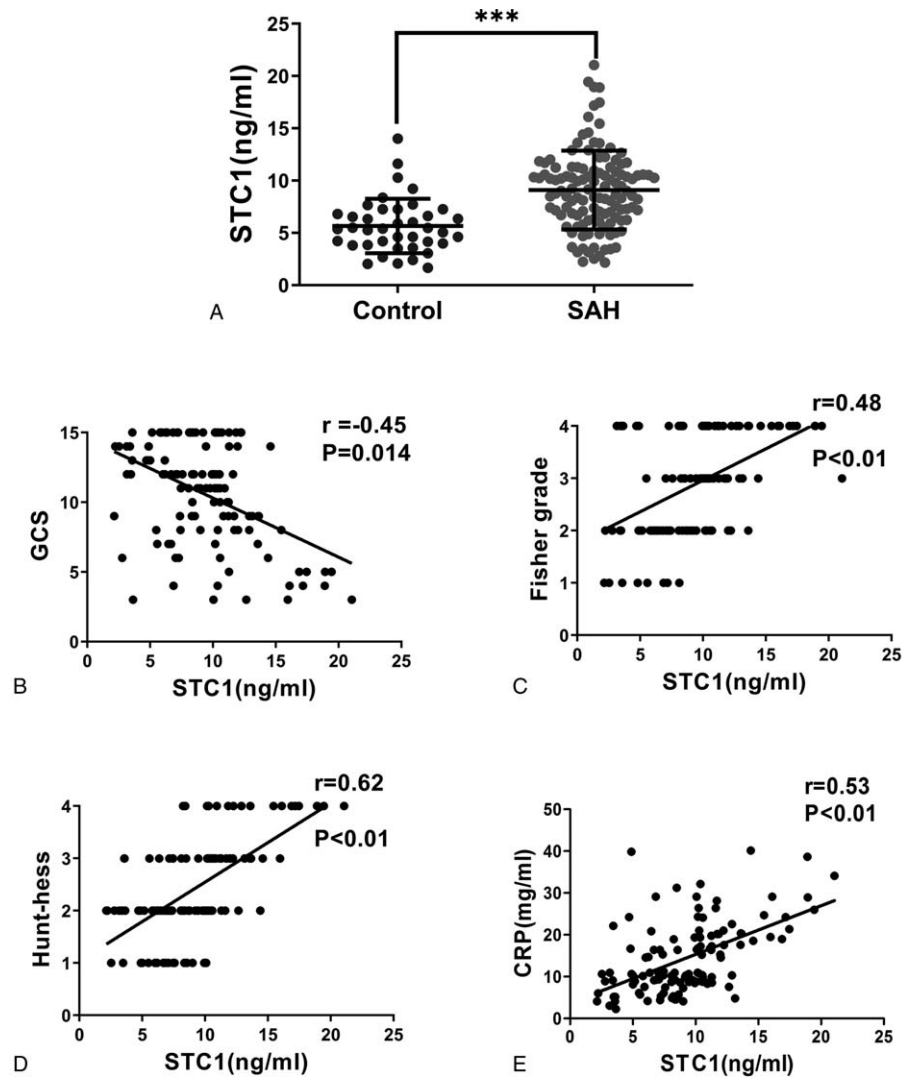


Figure 1. Serum level of STC1 change after aSAH. A, Level of STC1 in healthy controls and patients with SAH, ***, $P < .01$. B–E, Correlations between STC1 level and clinical severity (GCS, Fisher grade, Hunt-hess grade, and CRP level, respectively). CRP = C-reactive protein, GCS = Glasgow coma scale, STC1 = Stanniocalcin 1.

Clinical predictive models that combined serum biomarker and scales were more reliable than simply relying on validated scales. Proenkephalin A was elevated in aSAH patients compared with healthy controls and the expression of Proenkephalin A was associated with increased WFNS score. Plasma Proenkephalin A

was similar to WFNS in predicting poor outcome of aSAH patients, but it improved the predictive ability of WFNS when they combined together.^[25] Another study found that high-mobility group box 1, a DNA binding protein, could improve the AUC of modified Fisher grade and WFNS in predicting outcome

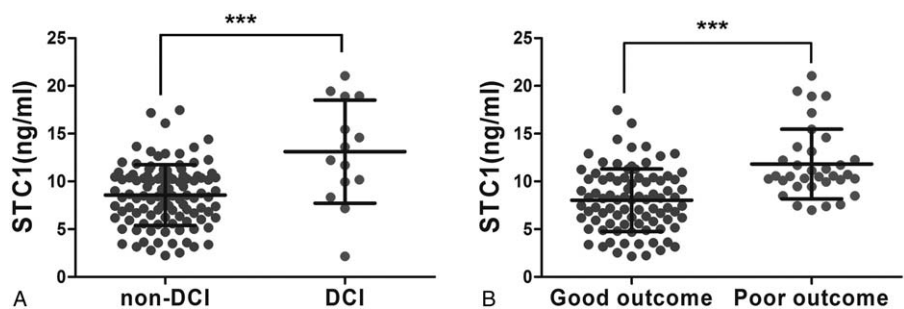


Figure 2. Association between serum STC1 and clinical outcome. STC1 = stanniocalcin 1; ***, $P < .01$.

Table 2

Univariate and multivariate logistic regression analysis of risk factors associated with poor outcome.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age>60 yr	1.08 (0.49–2.39)	.85	—	—
Male	1.56 (0.69–3.54)	.48	—	—
Hypertension	1.56 (0.69–3.53)	.29	—	—
Current smoking	0.40 (0.08–1.88)	.25	—	—
Diabetes	2.84 (1.15–7.04)	.02	1.44 (0.45–4.59)	.54
GCS>9	0.86 (0.34–2.16)	.74	—	—
Intraventricular hemorrhage	2.06 (0.89–4.37)	.48	—	—
Fisher grade III–IV	1.36 (0.60–3.09)	.47	—	—
Hunt-hess grade III–IV	3.54 (1.54–5.14)	<.01	3.76 (1.38–10.27)	.01
Clipping	2.24 (1.07–4.38)	.62	—	—
STC1 (ng/mL)	3.40 (1.45–12.04)	<.01	1.32 (1.10–1.58)	<.01
CRP (mg/mL)	1.06 (1.07–1.11)	.02	0.99 (0.93–1.07)	.86

CRP = C-reactive protein, GCS = Glasgow coma scale, STC1 = stanniocalcin 1.

Table 3

Univariate and multivariate logistic regression analysis of risk factors associated with DCI.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age>60 yr	0.92 (0.084–1.05)	.64	—	—
Male	1.34 (0.87–2.13)	.38	—	—
Hypertension	1.15 (0.62–2.08)	.67	—	—
Current smoking	0.62 (0.38–1.68)	.08	0.58 (0.26–0.87)	.71
Diabetes	3.01 (1.28–6.51)	<.01	1.85 (0.61–3.07)	.45
GCS>9	0.64 (0.55–1.37)	.86	—	—
Intraventricular hemorrhage	2.64 (0.94–3.26)	.13	—	—
Fisher grade III–IV	2.17 (0.97–5.63)	.04	2.34 (1.17–6.22)	.02
Hunt-hess grade III–IV	4.21 (1.27–8.62)	<.01	4.10 (1.88–12.37)	<.01
Clipping	0.67 (0.31–1.08)	.59	—	—
STC1 (ng/mL)	2.03 (1.28–9.31)	<.01	1.64 (1.24–1.96)	<.01

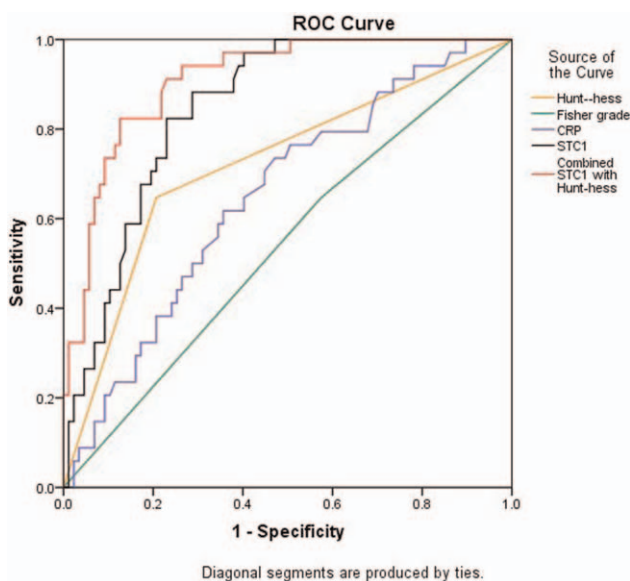


Figure 3. Value of variables in predicting poor outcome in patients with aSAH. CRP = C-reactive protein, GCS = Glasgow coma scale, ROC = receiver operating curve, STC1 = stanniocalcin 1.

of aSAH in a combined logistic-regression model.^[26] Besides, by using a combined logistic-regression model, Zhu et al found that copeptin improved the AUC of WFNS score in the prediction clinical outcome of aSAH patients, which indicated that copeptin was a complementary biomarker in predicting outcome of aSAH patients.^[27] The results in other studies were not the same with these. Plasma adrenomedullin concentration was elevated in patients who died or had poor outcome and it had the similar predictive ability to WFNS score according to ROC curves. But plasma adrenomedullin had no additional benefit on improving predictive power of WFNS in a combined logistic-model.^[29] Another study achieved similar results. Scd40L had the similar value to WFNS score in predicting outcome of aSAH patients, but failed to improve the predictive value of WFNS score in a combined logistic-model.^[30] In this study, we combined STC1 with Hunt-hess together to predict outcome of aSAH patients. Our results revealed that STC1 improved the predictive accuracy of Hunt-hess in aSAH patients, which indicated that STC1 was a novel and complementary biomarker in predicting outcome of patients with aSAH.

There were some limitations in this study. The number of patients included in this study was relatively small. Besides, the expression of STC1 might be caused by surgical operation, which we have not taken into consideration in this study. Clinical

prediction models that contain multiple variables will be more reliable. So further study should be performed to investigate the role of STC1 in the clinical prediction model, which may be more reliable in predicting clinical outcome of aSAH patients.

Author contributions

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Writing – original draft: Qin Jun, weijian luo.

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