

Serum Secreted Protein Acidic and Rich in Cysteine-Like I as a Biochemical Predictor for Prognosticating Clinical Outcomes After Acute Supratentorial Intracerebral Hemorrhage: A Prospective Cohort Study

Jianjun Huang¹, Fangping Shao², Bin Chen¹, Guanrong Zheng¹, Jia Shen¹, Shenzhong Qiu¹

¹Department of Neurosurgery, The First People's Hospital of Fuyang District of Hangzhou City, Hangzhou, People's Republic of China; ²Emergency Department, The First People's Hospital of Fuyang District of Hangzhou City, Hangzhou, People's Republic of China

Correspondence: Shenzhong Qiu, Department of Neurosurgery, The First People's Hospital of Fuyang District of Hangzhou City, Hangzhou, People's Republic of China, Email chengiftboy@163.com

Background: Secreted protein acidic and rich in cysteine-like 1 (SPARCL1) regulates synaptic stability and is up-regulated during axonal regeneration. Here, serum SPARCL1 was determined for estimating severity and prognosticating early neurological deterioration (END) and functional outcomes of acute intracerebral hemorrhage (ICH).

Methods: In this prospective observational cohort study of 156 patients with supratentorial ICH, blood samples of 53 were acquired not only at admission but also at days 1, 3, 5, 7 and 10. Another group of 53 healthy controls were recruited. The modified Rankin Scale (mRS) scores of 3–6 at poststroke six months were regarded as poor prognosis.

Results: As opposed to controls, serum SPARCL1 levels were markedly elevated during the early ten days after ICH, with the highest levels at days 1 and 3. Admission serum SPARCL1 levels were independently correlated with National Institutes of Health Stroke Scale scores and hematoma volume, were significantly increased in the order of six-month mRS scores from 0 to 6 and were independently correlated with six-month mRS scores. Serum SPARCL1 levels were linearly related to risks of poor six-month prognosis and END under restricted cubic spline, had significant efficiency under receiver operating characteristic (ROC) curve and were independently associated with END and poor prognosis. Subgroup analysis confirmed that no interactions existed for associations of serum SPARCL1 levels with other variables, such as age, gender and some specific vascular risk factors. END and poor prognosis prediction models integrating serum SPARCL1 were displayed using the two nomograms. The poor prognosis prediction model, but END prediction model not, performed well under calibration curve, decision curve and ROC curve.

Conclusion: A substantial elevation of serum SPARCL1 levels during the early period after ICH is independently related to illness severity and poor neurological outcomes, thus signifying that serum SPARCL1 may appear as a prognostic biomarker of ICH.

Keywords: Secreted protein acidic and rich in cysteine-like 1, intracerebral hemorrhage, early neurologic deterioration, prognosis, severity, biomarkers

Introduction

Spontaneous intracerebral hemorrhage (ICH) is universally recognized as a very common cerebrovascular illness, and its mortality ranks the first among all brain strokes, including ischemic stroke and spontaneous subarachnoid hemorrhage.¹ Acute lobar bleedings present a different clinical profile and a more severe early prognosis than acute deep subcortical hemorrhages and a non-hypertensive mechanism, namely cerebral amyloid angiopathy, predominates in the lobar location.² During ICH, bleedings directly enter into the brain parenchyma, thereby destroying brain tissues.³ Alternatively, secondary brain injury is abruptly initialized, and a series of cascading events, including inflammatory

reaction, oxidative response and cellular death, were promptly activated.⁴ Altogether, all brain injuries may lead to permanent neuronal destruction, subsequently damage neurological functions and even result in death among ICH patients.⁵ It is believable that early neurological deterioration (END) is very frequently observed during treatment for ICH and is closely relevant to poor prognosis of ICH patients.⁶ Undoubtedly, the National Institutes of Health Stroke Scale (NIHSS) is a very useful clinical severity scale, and hematoma volume is always applied in clinical work for estimating radiological severity of ICH.^{7,8} Noteworthy, a growing body of researchers have gradually paid close attention to the identification of some reliable biomarkers, which may shed light on the mechanisms of disease progression, as well as aid in severity assessment and prognosis prediction of ICH.^{9–11}

Secreted protein acidic and rich in cysteine-like 1 (SPARCL1), also named as HEVIN, is a kind of matricellular protein and in humans is encoded by the SPARCL1 gene.^{12–14} It has been well known that SPARCL1, which is highly expressed in both astrocytes and neurons of animal and human brains, may participate in neuronal migration and synaptogenesis during development, thereby supporting neuronal integrity.^{15–18} During axonal regeneration after brain injury, SPARCL1 was markedly upregulated and could influence synaptic stability.^{15,16} Also, SPARCL1's expressions were up-regulated dramatically in ischemic or hemorrhagic brain tissues of rats.¹⁹ Notably, there was a close correlation between serum SPARCL1 levels and severity indicated by baseline NIHSS score following acute ischemic stroke.²⁰ Alternatively, serum SPARCL1 levels were independently related to in-hospital mortality and admission traumatic severity reflected by Glasgow coma scale scores among patients with severe traumatic brain injury.²¹ Herein, our study was designed to ascertain longitudinal change of serum SPARCL1 levels after acute ICH and further to discern its association with long-term functional outcome and END in a cohort of humans with acute ICH.

Materials and Methods

Study Design and Ethical Approval

Between January 2019 and July 2022, a clinical observational analytical study was performed at the First People's Hospital of Fuyang District of Hangzhou City. This study included two sub-studies. The first sub-study was a cross-sectional study, in which serum SPARCL1 levels were gauged at admission and at days 1, 3, 5, 7 and 10 following ICH in ICH patients who were willing to accept blood collection at multiple time points; another group of healthy individuals were recruited as controls and serum SPARCL1 levels were measured at entry into study. This sub-study was aimed to explore dynamic change of serum SPARCL1 levels after ICH. The second sub-study was a prospective cohort study, in which admission serum SPARCL1 levels were detected in all ICH patients who consented to blood drawings at admission. This sub-study was designed to discover the role of serum SPARCL1 as a potential predictor of poor prognosis and END among patients with acute ICH. The current study complied with the guidelines of the Declaration of Helsinki and its amendments. Its protocol was endorsed by the Ethics Committee at the First People's Hospital of Fuyang District of Hangzhou City (No. FYD2019011). Signed informed consent forms were acquired from the patients' next of kins or controls themselves.

Participant Recruitments

All patients with ICH were consecutively recruited according to the enrollment criteria below: (1) age of eighteen years or older; (2) first-time ICH; (3) supratentorial bleedings; (4) primary ICH, but not including primary intraventricular hemorrhage; (5) non-surgical treatment for intracerebral hematoma; and (6) hospitalization within poststroke 24 hours. The exclusion criteria were: (1) other neurological diseases, such as strokes, tumors, infections, degenerative diseases and immune diseases; (2) other severe diseases in other organs, such as malignancies, liver cirrhosis, uremia, chronic obstructive pulmonary disease and ascites; and (3) some specific conditions, such as pregnancies, missed visits, incomplete data, refusal to participation and unavailable blood samples. Controls were composed of healthy physical examinees, who did not present with some chronic diseases, such as hypertension, chronic coronary disease and diabetes mellitus, as well as had normal results in conventional blood tests, such as leucocyte, glucose, sodium and creatinine.

Data Collections

The recorded demographical data were age and sex. The registered vascular risk factors included hypertension, diabetes mellitus, dyslipidemia, cigarette smoking and alcohol drinking. The collected specific medications were statins, anticoagulative agents and antiplatelet drugs. Hospital admission time was referred to as duration from the onset of stroke symptom to hospitalization. Blood-sampling time was deemed as duration between the stroke onset and blood-drawings. Arterial blood pressures, including systolic and diastolic, were determined non-invasively. Hematomas were divided into superficial and deep. Hematoma size was estimated by the equation $0.5 \times a \times b \times c$.²² We also observed intraventricular or subarachnoidal extension of hematoma via head computerized tomography scan. Baseline NIHSS was considered as a clinical severity indicator for reflecting neurological function. An enhancement of four points or more in NIHSS score or death within 24 h following admission signified END.²³ Poststroke six-month modified Rankin Scale (mRS) scores were estimated, the scores 3–6 meant a poor prognosis based on the neurological function status, and the score 6 indicates an all-cause death.²⁴

Sample Collection and Measurement of Serum SPARCL1 Levels

In accordance with patients' voluntary compliance principle, blood samples at admission could be obtained from all patients, and those at other time points (namely, at days 1, 3, 5, 7 and 10) were only acquired from a portion of patients. Controls' blood specimens were collected when agreeing with entrance into our study. Participants were phlebotomized via the antecubital vein. About 5 mL of drawn venous blood was at once put into a gel-containing biochemistry tube and, after clot formation, was spun at $2000 \times g$ for 10 min. Afterwards, the supernatants were separated and obtained serum samples were transferred into Eppendorf tubes and preserved at $-80\text{ }^{\circ}\text{C}$ refrigerator until further quantifications. Every three months, serum samples were thawed. For the quantitative measurement of SPARCL1 in human serum, a human SPARCL1 simple-step enzyme-linked immunosorbent assay kit (ab272478; Abcam) was applied. Its detection range changed between 39.06 pg/mL and 2500 pg/mL, detection sensitivity was 7.89 pg/mL, intra-assay coefficients of variation were $<10\%$ and inter-assay coefficients of variation were $<10\%$. In accordance with the manufacturer's instructions, the detections were done in duplicate by the same experienced practitioner, who was unaware of clinical data. The mean value of the two determinations were employed for further analysis.

Statistical Analysis

The used statistical softwares were SPSS software (version 23.0; SPSS Inc., Chicago, IL, USA) and R 3.5.1 software (<https://www.r-project.org>), and the utilized graphing software was GraphPad Prism 7.01 (GraphPad Software Inc., San Diego, California, USA). Qualitative data, which were summarized in form of frequencies (proportions), were compared between the two groups using the chi-square test or Fisher's exact test where appropriate. As for quantitative data, the Kolmogorov–Smirnov test was at first employed to discern normal distribution. They, if normally distributed, were presented as mean (standard deviation, SD) and if non-normally distributed, as median (25th – 75th percentiles). Their differences between the two groups were assessed using the independent-sample Student's *t*-test or Mann–Whitney *U*-test in accordance with data distribution patterns. Patients were divided into the two groups based on END occurrence and development of poor prognosis. Those factors, which were significantly different on univariate analyses, were entered into the binary multivariate logistic regression model to determine independent predictors of END and poor prognosis. The restricted cubic spline was constructed to investigate whether serum SPARCL1 levels were linearly correlated with risk of END or poor prognosis. Subgroup analysis was performed to determine whether interactions for associations existed between serum SPARCL1 levels and other factors, such as age, gender and some specific chronic diseases. Using the Kruskal–Wallis test, differences of serum SPARCL1 levels between controls and multiple time points of patients were ascertained. Friedman test was applied to describe temporal change of serum SPARCL1 levels following ICH. Using the Spearman test, bivariate correlations between serum SPARCL1 level and other variables, as well as between poststroke six-month mRS scores and other variables were evaluated. Therefore, the significantly correlated factors were forced into the multivariate linear regression model to determine variables, which were independently pertinent to mRS scores or serum SPARCL1 levels. Discriminatory efficiencies were assessed under the receiver operating characteristic (ROC) curve. Independent predictors of END and poor prognosis, which were derived from

multifactor analysis, were combined to form the two prediction models. The nomograms were plotted to describe the models. Furthermore, the models were evaluated using ROC curve analysis, decision curve analysis and calibration curve analysis. A two-sided $P < 0.05$ signified statistically significant difference.

Results

Participant Characteristics

During the study period, an aggregate of 204 consecutively enrolled adult patients with first-onset primary supratentorial brain hemorrhage, underwent conservative treatment for intracerebral hematoma within poststroke 24 hours at our hospital. Thereafter, we excluded 48 patients with other neurological diseases (17 cases), other severe diseases in other organs (21 cases) or some specific conditions (10 cases). Finally, one hundred and fifty-six patients were analyzed statistically.

Among this group of 156 patients, 53 patients had their blood-sample collections at multiple time-points. In addition, a total of 53 controls were selected for comparing serum SPARCL1 levels after acute ICH. This cohort of 53 patients were aged from 44 to 85 years (mean, 64.1 years; SD, 11.8 years) and contained 27 males and 26 females. This host of controls were aged from 40 to 88 years (mean, 63.1 years; SD, 12.8 years) and included 29 males and 24 females. By comparison, mean age and gender percentage insignificantly differed between that portion of patients and controls (both $P > 0.05$).

A total of 89 males and 67 females constituted this group of patients, who were aged from 42 to 85 years (mean, 61.7 years; SD, 11.2 years). As for vascular risk factors, hypertension, diabetes mellitus, dyslipidemia, cigarette smoking and alcohol drinking were found in 99, 34, 55, 60 and 66 patients, respectively. As regards specific medications, statins, anticoagulants and antiplatelet agents were orally taken by 45, 10, and 23 patients, respectively. Hospital admission time varied between 0.5 and 24.0 h (median, 8.5 h; percentiles 25th–75th, 5.5–14.3 h) since the onset of stroke symptom. Blood sampling time ranged from 1.5 to 26.0 h (median, 9.5 h; percentiles 25th–75th, 6.5–15.5 h) following stroke. Mean values of systolic arterial pressure and diastolic arterial pressure were 147.7 (range, 111–214 mmHg; SD, 23.4 mmHg) and 88.2 (range, 70–114 mmHg; SD, 9.8 mmHg), respectively. Concerning hematoma parameters, superficial hematomas, deep hematomas, intraventricular extension of hematoma and subarachnoidal extension of hematoma were revealed among 47, 109, 31 and 15 patients, respectively. NIHSS scores varied from 0 to 17 (median, 9; lower-upper quartiles, 6–11) and hematoma volume ranged from 2 to 39 mL (median, 10 mL; lower-upper quartiles, 6–21 mL).

Dynamic Change of Serum SPARCL1 Levels and Its Correlation with Illness Severity

In [Figure 1](#), in contrast to controls, serum SPARCL1 levels of patients were substantially elevated at admission, peaked at day 1, plateaued at day 3, and thereafter were gradually reduced at day 5 until day 10, which during six time points after ICH were still significantly higher than those of controls ($P < 0.001$).

Baseline serum SPARCL1 levels were tightly correlated with admission NIHSS scores ($P < 0.001$; [Figure 2A](#)) and hematoma volume ($P < 0.001$; [Figure 2B](#)). Alternatively, serum SPARCL1 levels were also related to the presence of diabetes mellitus, intraventricular extension of hematoma and blood glucose levels (all $P < 0.05$; [Table 1](#)). In the multivariate linear regression model, which incorporated NIHSS scores, hematoma volume, diabetes mellitus, intraventricular extension of hematoma and glucose levels, serum SPARCL1 levels were independently correlated with NIHSS scores (beta, 0.320; 95% confidence interval, 0.120–0.520; VIF, 2.633; $P = 0.002$) and hematoma volume (beta, 0.145; 95% confidence interval, 0.052–0.239; VIF, 2.814; $P = 0.002$).

Baseline Serum SPARCL1 Levels and Functional Outcome at Poststroke Six Months

Poststroke 6-month mRS scores varied from 0 to 6, with a median value of 2 (lower-upper quartiles, 2–4), and the scores from 0 to 6 were observed in 11, 21, 48, 26, 26, 10, and 14 patients, respectively. In [Figure 2C](#), serum SPARCL1 levels were dramatically positively related to mRS scores, which was deemed as a continuous variable ($P < 0.001$). And serum SPARCL1 levels were markedly elevated with increasing mRS scores from 0 to 6 ($P < 0.001$; [Figure 2D](#)). As listed in [Table 2](#), mRS scores had statistically significant correlation with age, intraventricular extension of hematoma, NIHSS

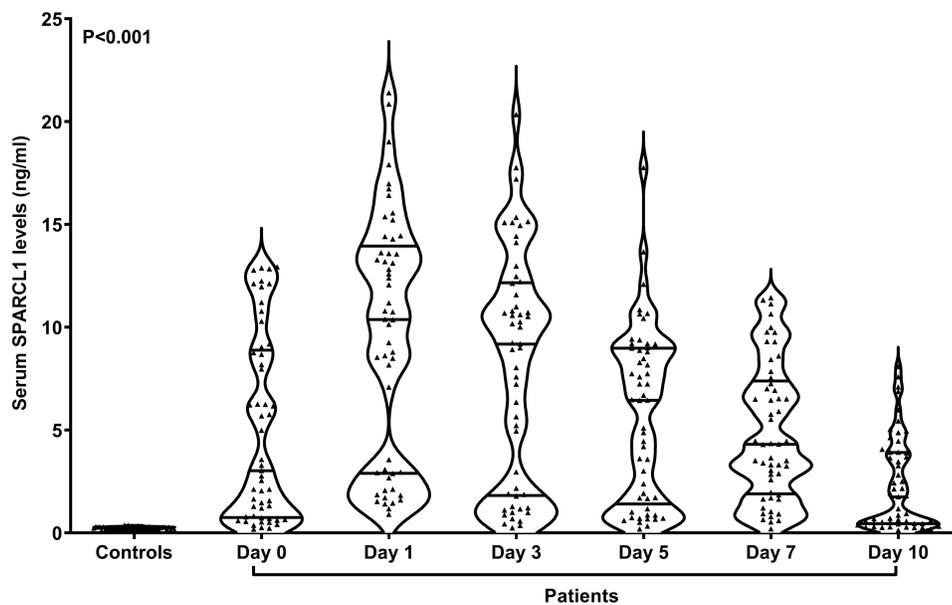


Figure 1 Serial changes of secreted protein acidic and rich in cysteine-like I levels in serum of patients with acute intracerebral hemorrhage. Serum secreted protein acidic and rich in cysteine-like I levels at admission and at days 1, 3, 5, 7 and 10 in patients were all substantially higher than those of controls, with the highest levels at days 1 and 3 after acute intracerebral hemorrhage among patients ($P<0.001$).

Abbreviation: SPARCL1, secreted protein acidic and rich in cysteine-like I.

scores, hematoma volume, blood glucose levels and serum SPARCL1 levels (all $P<0.05$). The abovementioned six factors were forced into the multivariate model and subsequently it was found that serum SPARCL1 levels (beta, 0.125; 95% confidence interval, 0.065–0.184; VIF, 1.649; $P=0.011$), NIHSS score (beta, 0.130; 95% confidence interval, 0.056–0.205; VIF, 2.660; $P=0.001$) and hematoma volume (beta, 0.069; 95% confidence interval, 0.025–0.113; VIF, 1.095; $P=0.002$) were independently correlated with poststroke six-month mRS scores.

In aggregate, seventy-six patients presented with poor prognosis (mRS scores of 3–6). As listed in Table 3, patients with a poor prognosis had substantially higher serum SPARCL1 levels than those with a good prognosis ($P<0.001$). Figure 3 shows that serum SPARCL1 levels efficiently predicted poor prognosis ($P<0.001$). Moreover, serum SPARCL1 levels above 2.04 ng/mL predicted poor prognosis with 88.16% sensitivity, 56.25% specificity, Youden index of 0.4441, positive predictive value of 65.7% and negative predictive value of 83.3%. As displayed in Figure 4, serum SPARCL1 levels were linearly correlated with risk of poor prognosis ($P=0.061$). As opposed to patients who presented with a good prognosis, those with a poor prognosis had significantly older age, a markedly higher proportion of intraventricular extension of hematoma, and substantially higher admission serum SPARCL1 levels, NIHSS scores, hematoma volume and blood glucose levels (all $P<0.05$; Table 3). The aforementioned significant variables were incorporated into the binary logistic regression model, and it was demonstrated that NIHSS scores (odds ratio, 1.312; 95% confidence interval, 1.116–1.542; $P=0.001$), hematoma volume (odds ratio, 1.098; 95% confidence interval, 1.017–1.149; $P=0.013$) and admission serum SPARCL1 levels (odds ratio, 1.132; 95% confidence interval, 1.006–1.275; $P=0.040$) emerged as the three independent predictors of poor prognosis. In Table 4, no interactions were found for associations of serum SPARCL1 levels with other variables, such as age, gender and chronic diseases (all $P>0.05$). Using independent predictors of poor prognosis, a prediction model was delineated in form of the nomogram (Figure 5). Under the calibration curve, the model kept stable (Figure 6). Under the decision curve, the model was of clinical effectiveness (Figure 7). Noteworthy, the model exhibited the strongest predictive efficiency, as compared with other variables and even combination of NIHSS scores and hematoma volume (all $P<0.05$; Figure 8).

Baseline Serum SPARCL1 Levels and Risk of END Following ICH

Totally, 41 patients experienced END. Table 5 shows that patients with END exhibited markedly higher serum SPARCL1 levels than the other remainders ($P<0.001$). As displayed in Figure 9, serum SPARCL1 levels significantly discriminated

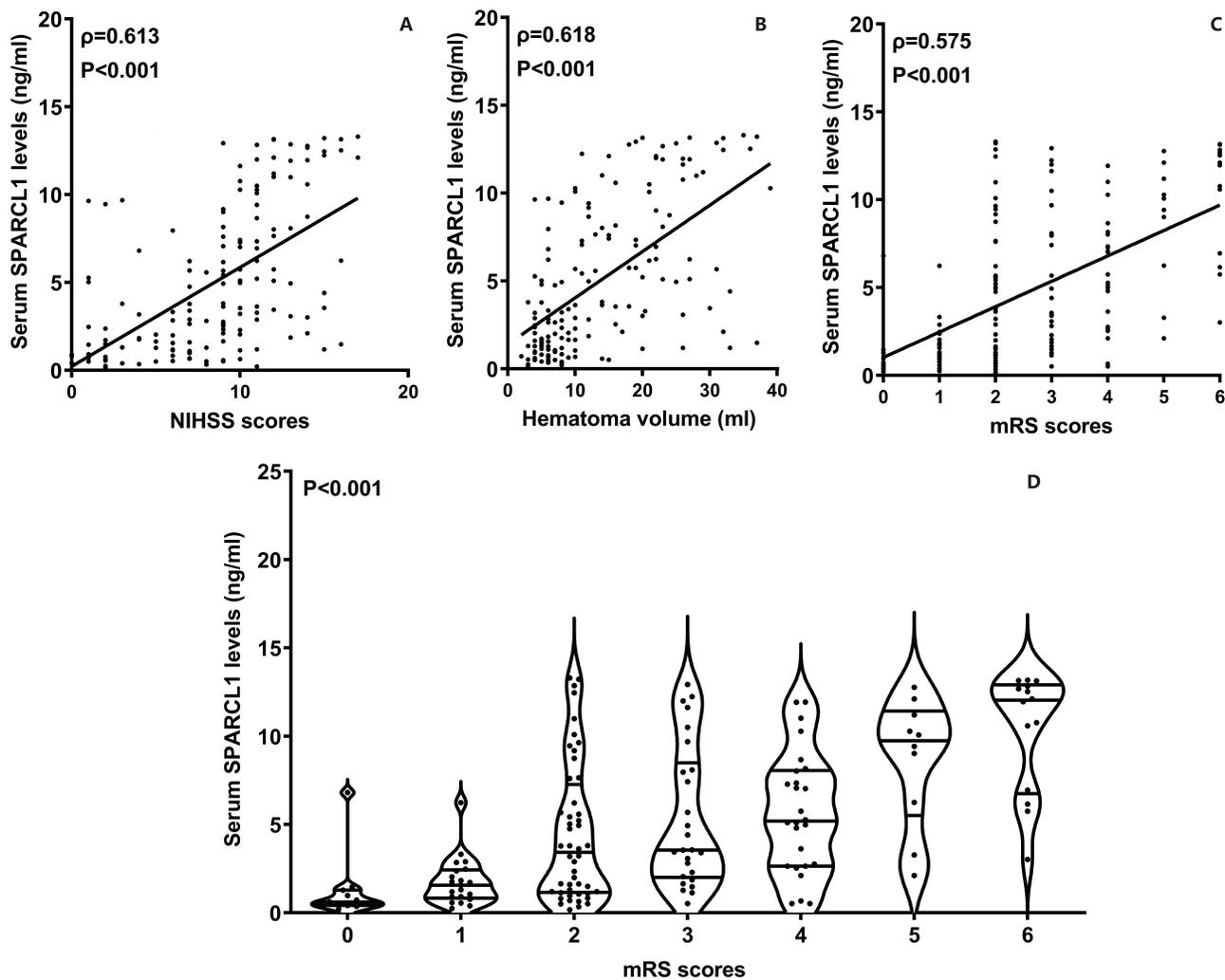


Figure 2 Relationship between serum secreted protein acidic and rich in cysteine-like I levels and severity in addition to six-month functional outcome after acute intracerebral hemorrhage in humans. **(A)**: Relationship between serum secreted protein acidic and rich in cysteine-like I levels and National Institutes of Health Stroke Scale scores after acute intracerebral hemorrhage in humans. Serum secreted protein acidic and rich in cysteine-like I levels were significantly correlative with National Institutes of Health Stroke Scale scores of patients with acute intracerebral hemorrhage ($P<0.001$). **(B)**: Relationship between serum secreted protein acidic and rich in cysteine-like I levels and hematoma volume of patients with acute intracerebral hemorrhage. Serum secreted protein acidic and rich in cysteine-like I levels had substantial correlation with hematoma volume following human acute intracerebral hemorrhage ($P<0.001$). **(C)**: Relation of serum secreted protein acidic and rich in cysteine-like I levels to modified Rankin scale scores at six months following acute intracerebral hemorrhage. There was a prominent correlation between serum secreted protein acidic and rich in cysteine-like I levels and poststroke six-month modified Rankin scale scores ($P<0.001$). **(D)**: Differences in terms of serum secreted protein acidic and rich in cysteine-like I levels among patients grouped based on modified Rankin scale scores at six months after acute intracerebral hemorrhage. Serum secreted protein acidic and rich in cysteine-like I levels were significantly lowest in patients with poststroke six-month modified Rankin scale score 0, followed by the scores from 1 to 5, and were substantially highest among those with the score 6 ($P<0.001$).

Abbreviations: SPARCL1, secreted protein acidic and rich in cysteine-like I; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale.

patients at risk of END ($P<0.001$). Moreover, serum SPARCL1 levels above 2.90 ng/mL predicted END with 85.37% sensitivity, 54.78% specificity, Youden index of 0.4015, positive predictive value of 40.2% and negative predictive value of 91.3%. Alternatively, there was a linear relationship between serum SPARCL1 levels and the END risk under restricted cubic spline ($P=0.286$; Figure 10). In comparison to patients without the development of END, those with END showed substantially higher admission serum SPARCL1 levels, NIHSS scores, hematoma volume and blood glucose levels (all $P<0.05$; Table 5). The abovementioned significant variables were forced into the binary logistic regression model, and it was verified that NIHSS scores (odds ratio, 1.189; 95% confidence interval, 1.047–1.350; $P=0.008$) and admission serum SPARCL1 levels (odds ratio, 1.117; 95% confidence interval, 1.004–1.243; $P=0.042$) appeared as the two independent predictors of END. In Table 6, no interactions existed between serum SPARCL1 levels and other variables, such as age, gender and chronic diseases (all $P>0.05$). Using independent predictors (ie, serum

Table 1 Correlation Analysis of Serum Secreted Protein Acidic and Rich in Cysteine-Like I Levels After Acute Intracerebral Hemorrhage

Variables	Spearman Test	
	ρ	P value
Age (years)	0.042	0.605
Gender (male/female)	-0.074	0.360
Hypertension	0.020	0.802
Diabetes mellitus	0.202	0.011
Dyslipidemia	0.075	0.353
Cigarette consumption	0.023	0.772
Alcohol consumption	-0.073	0.362
Previous statin use	0.014	0.859
Previous anticoagulant use	0.124	0.122
Previous antiplatelet use	0.048	0.552
Hospital admission time (h)	0.008	0.926
Blood sampling time (h)	0.015	0.848
Systolic arterial pressure (mmHg)	-0.132	0.100
Diastolic arterial pressure (mmHg)	0.009	0.913
Hemorrhagic locations (superficial/deep)	-0.034	0.677
Intraventricular extension of hematoma	0.210	0.009
Subarachnoidal extension of hematoma	0.122	0.128
National Institutes of Health Stroke Scale scores	0.613	< 0.001
Hematoma volume (mL)	0.618	< 0.001
Blood leucocyte count ($\times 10^9/l$)	0.112	0.164
Blood glucose levels (mmol/l)	0.170	0.034

Table 2 Correlation Analysis of Six-Month Modified Rankin Scale Scores After Acute Intracerebral Hemorrhage

Variables	Spearman Test	
	ρ	P value
Age (years)	0.198	0.013
Gender (male/female)	-0.118	0.142
Hypertension	0.003	0.966
Diabetes mellitus	0.098	0.225
Dyslipidemia	0.039	0.630
Cigarette consumption	-0.032	0.696
Alcohol consumption	-0.129	0.107
Previous statin use	0.019	0.811
Previous anticoagulant use	0.048	0.549
Previous antiplatelet use	-0.079	0.330
Hospital admission time (h)	-0.017	0.830
Blood sampling time (h)	-0.013	0.874
Systolic arterial pressure (mmHg)	-0.074	0.361
Diastolic arterial pressure (mmHg)	0.021	0.793
Hemorrhagic locations (superficial/deep)	0.035	0.664
Intraventricular extension of hematoma	0.187	0.019
Subarachnoidal extension of hematoma	0.107	0.185
National Institutes of Health Stroke Scale scores	0.598	< 0.001
Hematoma volume (mL)	0.590	< 0.001

(Continued)

Table 2 (Continued).

Variables	Spearman Test	
	ρ	P value
Blood leucocyte count ($\times 10^9/l$)	-0.008	0.919
Blood glucose levels (mmol/l)	0.259	0.001
Serum secreted protein acidic and rich in cysteine-like I levels (ng/mL)	0.575	<0.001

Table 3 Factors Related to Poor Prognosis at Six Months After Acute Intracerebral Hemorrhage

Variables	Modified Rankin Scale Scores		
	Scores 3–6	Scores 0–2	P value
Age (years)	63.7 \pm 9.7	59.8 \pm 12.1	0.026
Gender (male/female)	40/36	49/31	0.277
Hypertension	48 (63.2%)	51 (63.8%)	0.939
Diabetes mellitus	19 (25.0%)	15 (18.8%)	0.345
Dyslipidemia	30 (39.5%)	25 (31.3%)	0.283
Cigarette consumption	28 (36.8%)	32 (40.0%)	0.685
Alcohol consumption	28 (36.8%)	38 (47.5%)	0.178
Previous statin use	23 (30.3%)	22 (27.5%)	0.703
Previous anticoagulant use	6 (7.9%)	4 (4.6%)	0.341
Previous antiplatelet use	9 (11.8%)	14 (17.5%)	0.221
Hospital admission time (h)	8.5 (5.0–12.5)	9.5 (5.5–16.5)	0.202
Blood sampling time (h)	9.5 (6.3–13.5)	10.5 (6.5–17.8)	0.225
Systolic arterial pressure (mmHg)	147.0 \pm 23.6	148.4 \pm 23.3	0.718
Diastolic arterial pressure (mmHg)	88.4 \pm 10.6	88.0 \pm 9.0	0.772
Hemorrhagic locations (superficial/deep)	24/52	23/57	0.700
Intraventricular extension of hematoma	20 (26.3%)	11 (13.8%)	0.049
Subarachnoidal extension of hematoma	10 (13.2%)	5 (6.3%)	0.144
National Institutes of Health Stroke Scale scores	11.0 (9.0–12.5)	6.5 (2.5–9.0)	< 0.001
Hematoma volume (mL)	18.0 (10.5–23.0)	6.5 (4.5–10.5)	< 0.001
Blood leucocyte count ($\times 10^9/l$)	7.5 (4.9–9.6)	7.0 (5.3–9.0)	0.984
Blood glucose levels (mmol/l)	9.9 (7.8–15.0)	9.3 (7.9–10.9)	0.038
Serum secreted protein acidic and rich in cysteine-like I levels (ng/mL)	6.6 (3.1–10.7)	1.7 (0.9–5.0)	< 0.001

Notes: Data were presented as count (percentage), mean \pm standard deviation or median (upper-lower quartiles). The Chi-square test, Fisher exact test, Student's *t*-test or Mann-Whitney test was used for intergroup comparison.

SPARCL1 level and NIHSS scores) to configure a nomogram (Figure 11), the model was comparatively stable under the calibration curve (Figure 12) and was relatively clinically valuable under the decision curve (Figure 13). Disappointedly, the model exhibited the insignificantly higher predictive efficiency, in contrast to other variables (all $P > 0.05$; Figure 14).

Discussion

In this study of ICH patients, multiple multivariate models were configured, so that some interesting results were found. First, ICH patients, in contrast to healthy controls, had a significant elevation of serum SPARCL1 levels, with the highest levels at days 1 and 3 and the higher levels persisting at least until day 10 after stroke. Second, serum SPARCL1 levels were not only independently correlated with admission NIHSS scores and hematoma volume but also with poststroke six-month mRS scores. Third, serum SPARCL1 emerged as an independent predictor of six-month poor prognosis and END. Last, the model containing serum SPARCL1 performed well in predicting poor prognosis at six months after acute

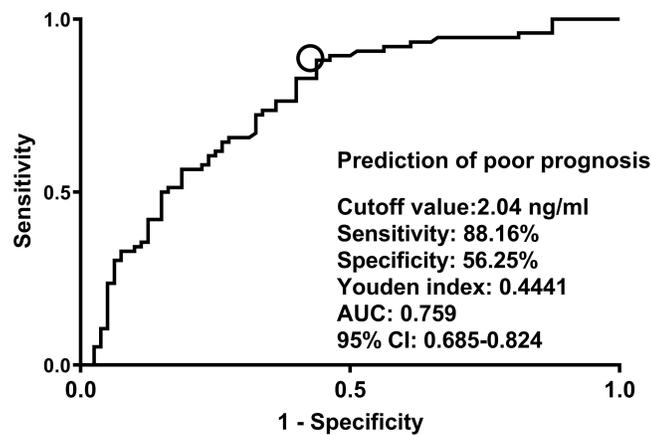


Figure 3 Ability with respect to serum secreted protein acidic and rich in cysteine-like I levels for predicting a poor prognosis at six months following acute intracerebral hemorrhage. Under the receiver operating characteristic curve, serum secreted protein acidic and rich in cysteine-like I levels efficiently distinguished the risk of a poor prognosis at 6 months after acute intracerebral hemorrhage ($P < 0.001$). Using the Youden method, a suitable value of serum secreted protein acidic and rich in cysteine-like I levels was selected, with the corresponding sensitivity and specificity values. Circle indicates the cutoff value.

Abbreviations: AUC, area under curve; 95% CI, 95% confidence interval.

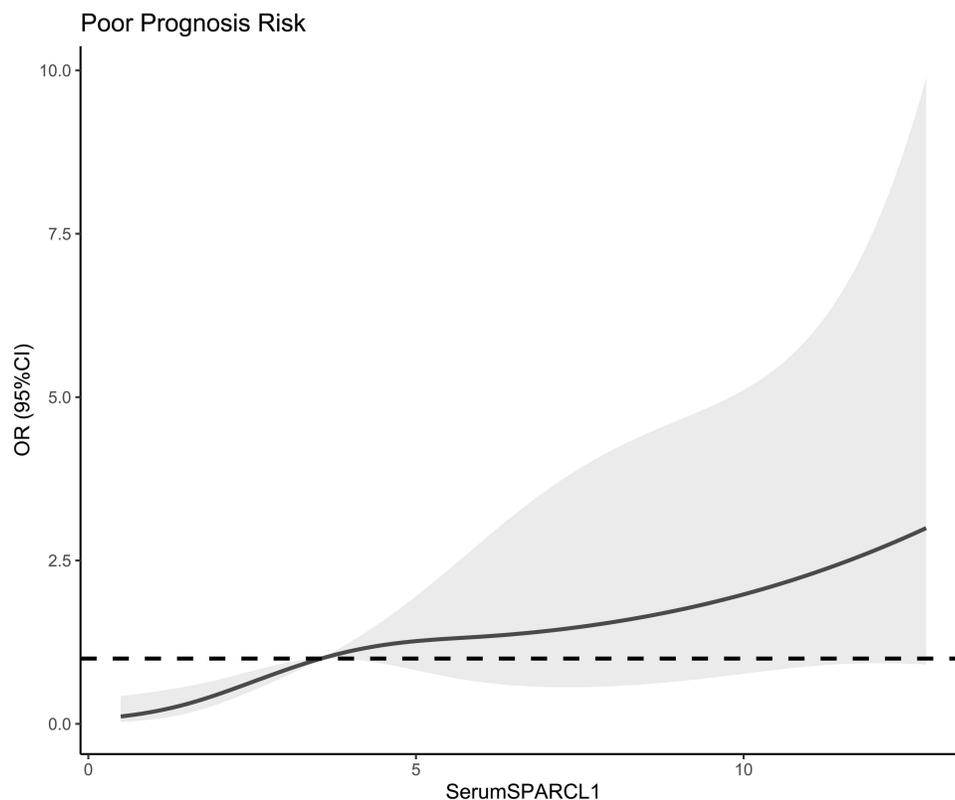


Figure 4 Restricted cubic spline showing relationship between serum secreted protein acidic and rich in cysteine-like I levels and risk of a poor prognosis at six months following acute intracerebral hemorrhage. There was a linear correlation between serum secreted protein acidic and rich in cysteine-like I levels and risk of a poor prognosis at six months following acute intracerebral hemorrhage ($P > 0.05$).

Abbreviations: SPARCL1, secreted protein acidic and rich in cysteine-like I; OR, odds ratio; 95% CI, 95% confidence interval.

ICH. Such data were strongly supportive of the presumption that serum SPARCL1 may be useful in prognosticating functional outcome of patients with ICH.

SPARCL1 is an antiadhesive glycoprotein and functions as the extracellular protein.^{12–14} It can regulate cell–matrix interactions and participates in tissue remodeling.^{25–27} Compelling evidence has confirmed that matricellular proteins are

Table 4 Subgroup Analysis for the Association of Serum Secreted Protein Acidic and Rich in Cysteine-Like I Levels with 6-Month Poor Prognosis After Acute Intracerebral Hemorrhage and Interaction Analysis Between Subgroups

Subgroup Analysis		Total (n)	OR (95% CI)	P value	P Interaction value
Age	≥ 61.7 years	85	1.200 (1.044–1.379)	0.010	0.336
	< 61.7 years	71	1.154 (1.007–1.324)	0.040	
Gender	Male	89	1.200 (1.022–1.407)	0.026	0.135
	Female	67	1.134 (0.994–1.294)	0.061	
Hypertension	Yes	99	1.192 (1.063–1.337)	0.003	0.367
	No	57	1.261 (1.023–1.554)	0.030	
Diabetes mellitus	Yes	34	1.217 (1.002–1.478)	0.048	0.727
	No	122	1.174 (1.030–1.339)	0.016	
Dyslipidemia	Yes	55	1.208 (1.031–1.416)	0.019	0.190
	No	101	1.188 (1.017–1.388)	0.030	
Cigarette consumption	Yes	60	1.199 (0.973–1.479)	0.089	0.346
	No	96	1.171 (1.022–1.341)	0.023	
Alcohol consumption	Yes	66	1.162 (0.947–1.426)	0.151	0.825
	No	90	1.133 (0.970–1.322)	0.115	
Previous statin use	Yes	45	0.975 (0.773–1.231)	0.833	0.086
	No	111	1.225 (1.058–1.420)	0.007	
Previous anticoagulant use	Yes	10	1.038 (0.716–1.504)	0.843	0.298
	No	146	1.177 (1.043–1.329)	0.008	
Previous antiplatelet use	Yes	23	1.187 (0.866–1.626)	0.287	0.398
	No	133	1.157 (1.013–1.321)	0.031	
Hospital admission time	≥ 8.5 h	87	1.391 (1.149–1.684)	0.001	0.231
	< 8.5 h	69	1.176 (0.961–1.439)	0.115	
Blood sampling time	≥ 9.5 h	87	1.127 (0.977–1.300)	0.100	0.174
	< 9.5 h	69	1.208 (1.017–1.435)	0.032	
Systolic arterial pressure	≥ 147.7 mmHg	56	1.187 (0.921–1.530)	0.185	0.467
	< 147.7 mmHg	100	1.128 (0.987–1.289)	0.077	
Diastolic arterial pressure	≥ 88.2 mmHg	64	1.131 (0.914–1.399)	0.257	0.379
	< 88.2 mmHg	92	1.140 (0.991–1.311)	0.066	
Hemorrhagic locations (superficial/deep)	Superficial	47	1.240 (0.991–1.551)	0.060	0.485
	Deep	109	1.143 (1.007–1.297)	0.039	
Intraventricular extension of hematoma	Yes	31	1.073 (0.899–1.294)	0.463	0.054
	No	125	1.172 (1.027–1.337)	0.019	
Subarachnoidal extension of hematoma	Yes	15	1.756 (0.872–3.537)	0.115	0.300
	No	141	1.126 (1.004–1.262)	0.042	
National Institutes of Health Stroke Scale scores	≥ 9	90	1.284 (1.006–1.640)	0.040	0.229
	< 9	66	1.344 (1.041–1.734)	0.023	
Hematoma volume	≥ 10 mL	86	1.199 (1.026–1.400)	0.022	0.114
	< 10 mL	70	1.341 (1.080–1.666)	0.008	
Blood leucocyte count	≥ 7.1 ×10 ⁹ /l	81	1.231 (1.012–1.499)	0.038	0.315
	< 7.1 ×10 ⁹ /l	75	1.206 (1.013–1.436)	0.036	
Blood glucose levels (mmol/l)	≥ 9.6 mmol/l	78	1.143 (0.967–1.350)	0.116	0.602
	< 9.6 mmol/l	78	1.293 (1.006–1.661)	0.045	

Notes: Associations were adjusted for age, National Institutes of Health Stroke Scale scores, hematoma volume, intraventricular extension of hematoma and blood glucose levels. During subgroup analysis, patients were dichotomized based on the median or mean value of each variable.

the important regulators of neuronal integrity.^{28–30} As such, SPARCL1 could impact synaptic stability and may play a pivotal effect in axonal regeneration after acute brain injury.^{31,32} Experimental data have shown that SPARCL1 in central nervous system was mainly localized in astrocytes under physiological conditions.¹⁵ In human brains, this protein was also observed.^{17,18} Moreover, its expressions by astrocytes were obviously upregulated in rats after transient ischemic stroke.¹⁶ Whether in ischemic stroke or intracerebral hemorrhage rats, SPARCL1 expressions were prominently

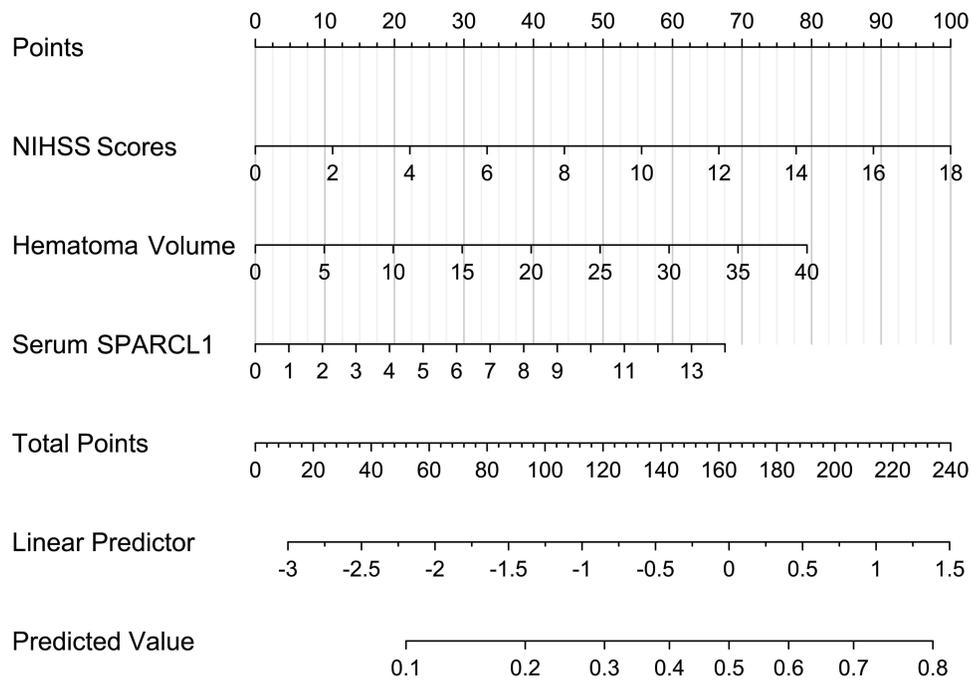


Figure 5 Nomogram predicting a poor prognosis at six months following acute intracerebral hemorrhage. Serum secreted protein acidic and rich in cysteine-like I, hematoma volume and National Institutes of Health Stroke Scale scores were integrated to predict a poor prognosis at six months following acute intracerebral hemorrhage. **Abbreviations:** SPARCL1, secreted protein acidic and rich in cysteine-like I; NIHSS, National Institutes of Health Stroke Scale.

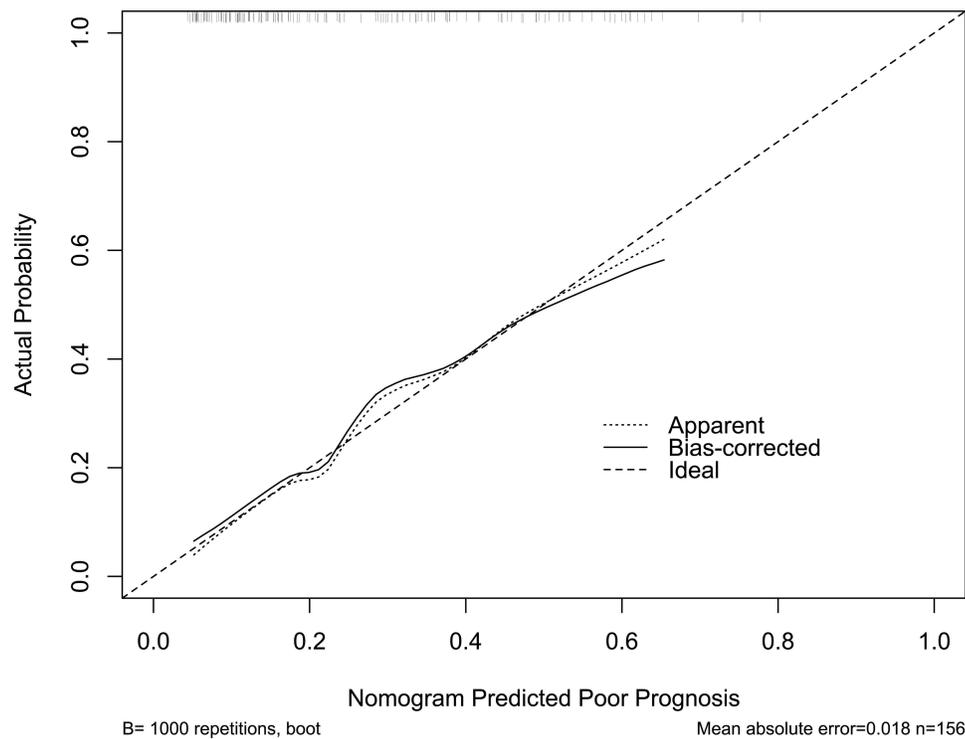


Figure 6 Calibration curve verifying stability of nomogram for predicting a poor prognosis at poststroke six months. The constructed prognosis prediction model was of comparative stability.

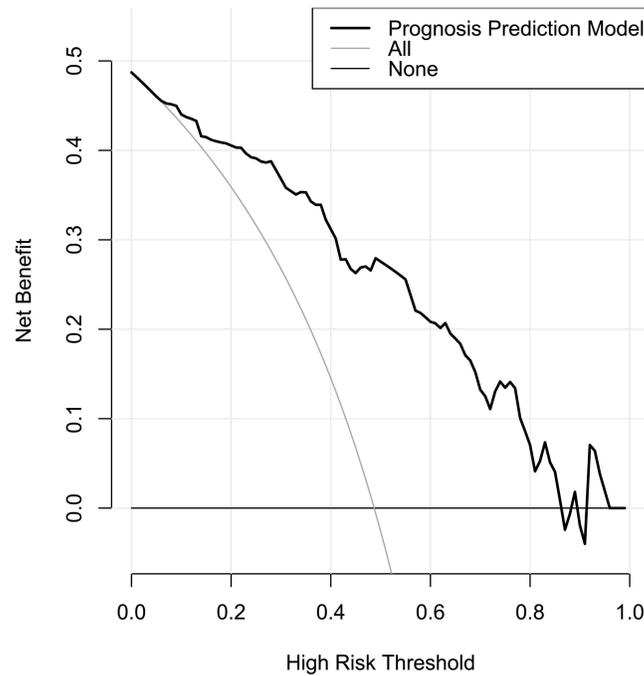


Figure 7 Decision curve validating clinical usability of nomogram in discriminating risk of a prognosis at poststroke six months. The configured prognosis prediction model was of relative efficiency in clinical work.

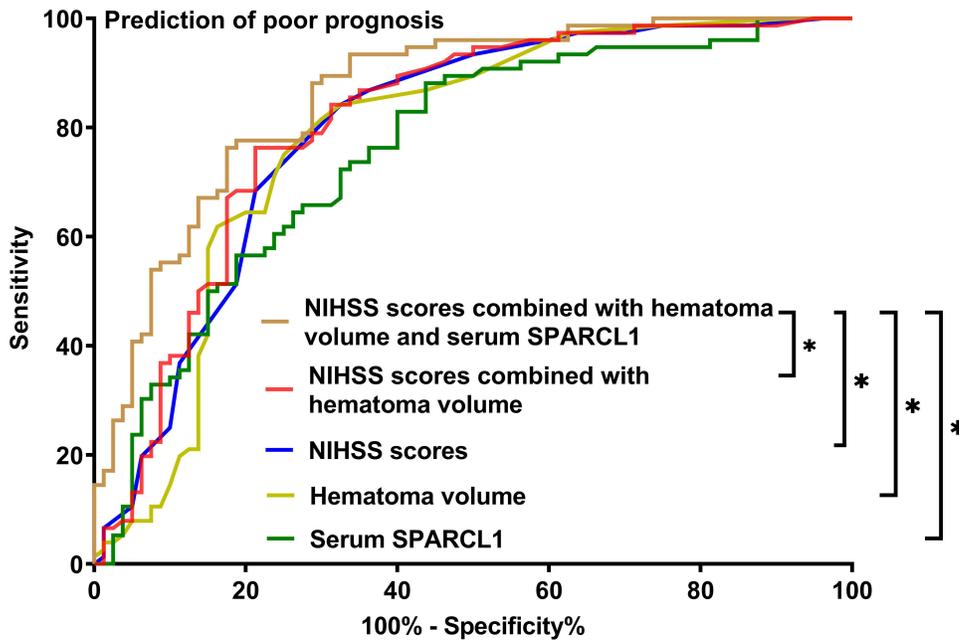


Figure 8 Differences in terms of prognosis prediction abilities between the built prognosis prediction model and other variables under the receiver operating characteristic curve. As compared to other variables, including combination of National Institutes of Health Stroke Scale scores with hematoma volume, National Institutes of Health Stroke Scale, hematoma volume and serum secreted protein acidic and rich in cysteine-like I, the prognosis prediction model integrating all of them showed significantly higher area under curve (all * $P < 0.05$).

Abbreviations: SPARCL1, secreted protein acidic and rich in cysteine-like I; NIHSS, National Institutes of Health Stroke Scale.

increased in injured brain tissues.¹⁹ Notably, SPARCL1 immunoreactivity was also verified in human cerebrospinal fluid and serum samples, but was absent from any blood cell type.¹⁸ Such a clue indicates that SPARCL1 may be a brain-specific protein. In other words, SPARCL1 could be considered as a potential biomarker for reflecting severity and

Table 5 Factors in Relation to Early Neurologic Deterioration After Acute Intracerebral Hemorrhage

Variables	Early Neurologic Deterioration		
	Presence	Absence	P values
Age (years)	60.8±9.6	62.0±11.7	0.541
Gender (male/female)	25/16	64/51	0.554
Hypertension	27 (65.9%)	72 (62.6%)	0.711
Diabetes mellitus	13 (31.7%)	21 (18.3%)	0.073
Dyslipidemia	12 (29.3%)	43 (37.4%)	0.350
Cigarette consumption	17 (41.5%)	43 (37.4%)	0.645
Alcohol consumption	18 (43.9%)	48 (41.7%)	0.810
Previous statin use	10 (24.4%)	35 (30.4%)	0.463
Previous anticoagulant use	1 (2.4%)	9 (7.8%)	0.457
Previous antiplatelet use	8 (19.5%)	15 (13.1%)	0.316
Hospital admission time (h)	9.5 (7.0–19.5)	8.5 (5.3–12.5)	0.108
Blood sampling time (h)	10.5 (7.5–20.5)	9.5 (6.5–13.8)	0.136
Systolic arterial pressure (mmHg)	147.9±27.6	147.7±21.8	0.955
Diastolic arterial pressure (mmHg)	88.4±9.8	88.1±9.9	0.855
Hemorrhagic locations (superficial/deep)	12/29	35/80	0.889
Intraventricular extension of hematoma	10 (24.4%)	21 (18.3%)	0.398
Subarachnoidal extension of hematoma	5 (12.2%)	10 (8.7%)	0.542
National Institutes of Health Stroke Scale scores	11.0 (9.0–14.0)	8.0 (4.5–10.0)	< 0.001
Hematoma volume (mL)	20.0 (13.0–26.0)	8.0 (5.5–15.5)	< 0.001
Blood leucocyte count ($\times 10^9/l$)	8.1 (5.0–10.0)	7.0 (5.1–9.2)	0.466
Blood glucose levels (mmol/l)	11.6 (8.0–15.7)	9.3 (7.8–11.4)	0.028
Serum secreted protein acidic and rich in cysteine-like I levels (ng/mL)	7.4 (3.8–12.0)	2.6 (1.2–6.9)	<0.001

Notes: Data were presented as count (percentage), mean \pm standard deviation or median (upper-lower quartiles). The Chi-square test, Fisher exact test, Student's t-test or Mann-Whitney test was used for intergroup comparison.

predicting clinical outcome in brain injury diseases. Also, it is postulated that serum SPARCL1, which was revealed in this study to have its levels with a significant enhancement after acute ICH, may be derived from injured brain tissues.

In a study of patients with acute ischemic stroke, serum SPARCL1 concentrations were verified to be positively correlated with clinical severity, when patients were dichotomized into the two groups (namely, admission NIHSS scores

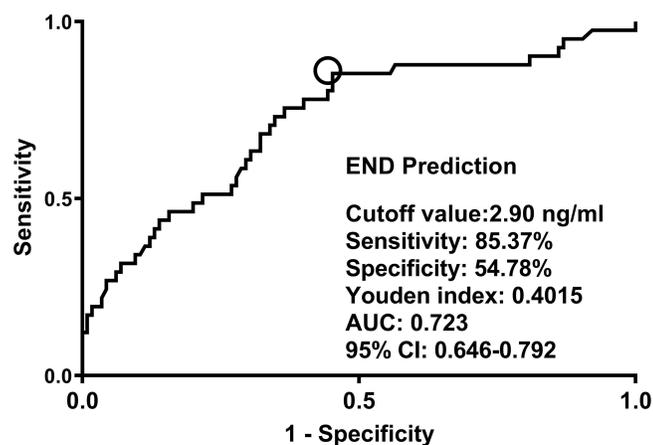


Figure 9 Capability with respect to serum secreted protein acidic and rich in cysteine-like I levels for predicting early neurological deterioration after acute intracerebral hemorrhage. Under the receiver operating characteristic curve, serum secreted protein acidic and rich in cysteine-like I levels efficiently distinguished the development of early neurologic deterioration after acute intracerebral hemorrhage ($P < 0.001$). Using the Youden method, a suitable value of serum secreted protein acidic and rich in cysteine-like I levels was yielded, with the corresponding sensitivity and specificity values. Circle indicates the cutoff value.

Abbreviations: AUC, area under curve; 95% CI, 95% confidence interval; END, early neurological deterioration.

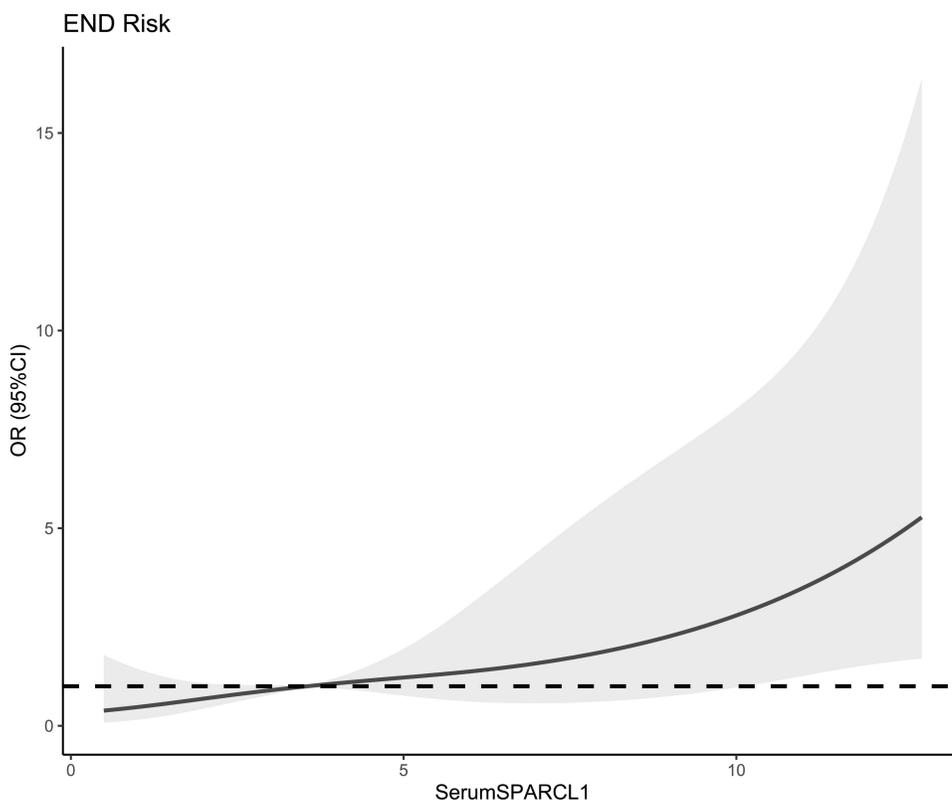


Figure 10 Restricted cubic spline displaying relationship between serum secreted protein acidic and rich in cysteine-like I levels and the development of early neurologic deterioration following acute intracerebral hemorrhage. There was a linear correlation between serum secreted protein acidic and rich in cysteine-like I levels and the development of early neurologic deterioration following acute intracerebral hemorrhage ($P>0.05$).

Abbreviations: SPARCL1, secreted protein acidic and rich in cysteine-like I; OR, odds ratio; 95% CI, 95% confidence interval; END, early neurologic deterioration.

<5 versus ≥ 6), and moreover, serum SPARCL1 was found to be an independent predictor for stroke severity (ie, admission NIHSS scores ≥ 6).²⁰ In another study of humans with severe traumatic brain injury, whether Glasgow coma scale was considered as a continuous variable, or transformed into a categorical variable, serum SPARCL1 levels were still independently related to Glasgow coma scale scores.²¹ Our study showed that serum SPARCL1 levels were independently correlated with NIHSS scores and hematoma volume after acute ICH. The above results may offer enough evidence to support the notion that SPARCL1 could be a promising serological marker for evaluating severity of acute brain injury diseases.

Table 6 Subgroup Analysis for the Association of Serum Secreted Protein Acidic and Rich in Cysteine-Like I Levels with Early Neurologic Deterioration After Acute Intracerebral Hemorrhage and Interaction Analysis Between Subgroups

Subgroup Analysis		Total (n)	OR (95% CI)	P value	P _{interaction} value
Age	≥ 61.7 years	85	1.100 (0.939–1.289)	0.273	0.429
	< 61.7 years	71	1.292 (1.052–1.587)	0.015	
Gender	Male	89	1.208 (1.027–1.421)	0.023	0.189
	Female	67	1.114 (0.971–1.277)	0.122	
Hypertension	Yes	99	1.346 (1.095–1.655)	0.005	0.297
	No	57	1.030 (0.879–1.208)	0.714	
Diabetes mellitus	Yes	34	1.243 (0.876–1.764)	0.223	0.136
	No	122	1.179 (1.026–1.355)	0.020	
Dyslipidemia	Yes	55	1.035 (0.798–1.342)	0.797	0.354
	No	101	1.425 (1.115–1.822)	0.005	

(Continued)

Table 6 (Continued).

Subgroup Analysis		Total (n)	OR (95% CI)	P value	P interaction value
Cigarette consumption	Yes	60	1.066 (0.920–1.236)	0.393	0.211
	No	96	1.235 (1.036–1.473)	0.019	
Alcohol consumption	Yes	66	1.064 (0.914–1.238)	0.424	0.201
	No	90	1.223 (1.019–1.467)	0.030	
Previous statin use	Yes	45	1.083 (0.959–1.222)	0.198	0.186
	No	111	1.205 (1.048–1.385)	0.009	
Previous anticoagulant use	Yes	10	1.111 (0.992–1.245)	0.069	0.098
	No	146	1.126 (1.009–1.256)	0.033	
Previous antiplatelet use	Yes	23	1.134 (0.953–1.349)	0.157	0.056
	No	133	1.150 (1.025–1.291)	0.017	
Hospital admission time	≥ 8.5 h	87	1.206 (1.042–1.396)	0.012	0.077
	< 8.5 h	69	1.189 (1.024–1.382)	0.023	
Blood sampling time	≥ 9.5 h	87	1.177 (0.913–1.518)	0.209	0.433
	< 9.5 h	69	1.123 (0.983–1.282)	0.088	
Systolic arterial pressure	≥ 147.7 mmHg	56	1.094 (0.909–1.316)	0.343	0.076
	< 147.7 mmHg	100	1.218 (1.049–1.414)	0.009	
Diastolic arterial pressure	≥ 88.2 mmHg	64	1.070 (0.896–1.277)	0.457	0.090
	< 88.2 mmHg	92	1.092 (1.017–1.172)	0.016	
Hemorrhagic locations (superficial/deep)	Superficial	47	1.050 (0.994–1.109)	0.083	0.134
	Deep	109	1.145 (1.008–1.301)	0.037	
Intraventricular extension of hematoma	Yes	31	1.101 (0.910–1.333)	0.322	0.344
	No	125	1.117 (1.025–1.216)	0.012	
Subarachnoid extension of hematoma	Yes	15	1.123 (0.998–1.263)	0.053	0.127
	No	141	1.137 (1.016–1.272)	0.026	
National Institutes of Health Stroke Scale scores	≥ 9	90	1.146 (1.028–1.279)	0.014	0.060
	< 9	66	1.145 (1.024–1.281)	0.017	
Hematoma volume	≥ 10 mL	86	1.103 (1.004–1.211)	0.041	0.080
	< 10 mL	70	1.131 (1.008–1.270)	0.036	
Blood leucocyte count	≥ 7.1 ×10 ⁹ /l	81	1.083 (1.008–1.165)	0.030	0.624
	< 7.1 ×10 ⁹ /l	75	0.992 (0.854–1.153)	0.919	
Blood glucose levels (mmol/l)	≥ 9.6 mmol/l	78	1.118 (0.995–1.257)	0.062	0.150
	< 9.6 mmol/l	78	1.264 (1.044–1.530)	0.016	

Notes: Associations were adjusted for National Institutes of Health Stroke Scale scores, hematoma volume and blood glucose levels. During subgroup analysis, patients were dichotomized based on the median or mean value of each variable.

There was a recent clinical epidemiological investigation showing that serum SPARCL1 levels were independently associated with in-hospital mortality in a cohort of patients with severe traumatic brain injury.²¹ Our study extended follow-up time to six months and neurological function, but not mortality, was assessed in this group of ICH patients. Serum SPARCL1 levels were independently correlated with mRS scores. Interestingly, serum SPARCL1 emerged as an independent predictor of END and poor prognosis (mRS scores of 3–6). Furthermore, the two prediction models, which contained serum SPARCL1 and other independent predictors of END and poor prognosis in this group of patients, were constructed. Via a series of statistical methods, including ROC curve, calibration curve and decision curve analyses, the prognosis prediction model performed well and may be of clinical value. Our study built the restricted cubic spline and performed subgroup analysis with interaction identification. So, the results may be more scientific and reliable. Overall, it is believably conceived that serum SPARCL1 may be a useful prognostic biomarker of acute ICH and its measurement may aid in clinical prognostication of long-term functional outcome following acute ICH.

There are several strengths and weaknesses in this study. The strengths are that (1) to the best of our knowledge, this is the first series for verifying relationships between serum SPARCL1 levels, severity, prognosis and END after ICH using multivariate analysis; (2) a cohort of patients with supratentorial ICH were selected, so that the sample homogeneity

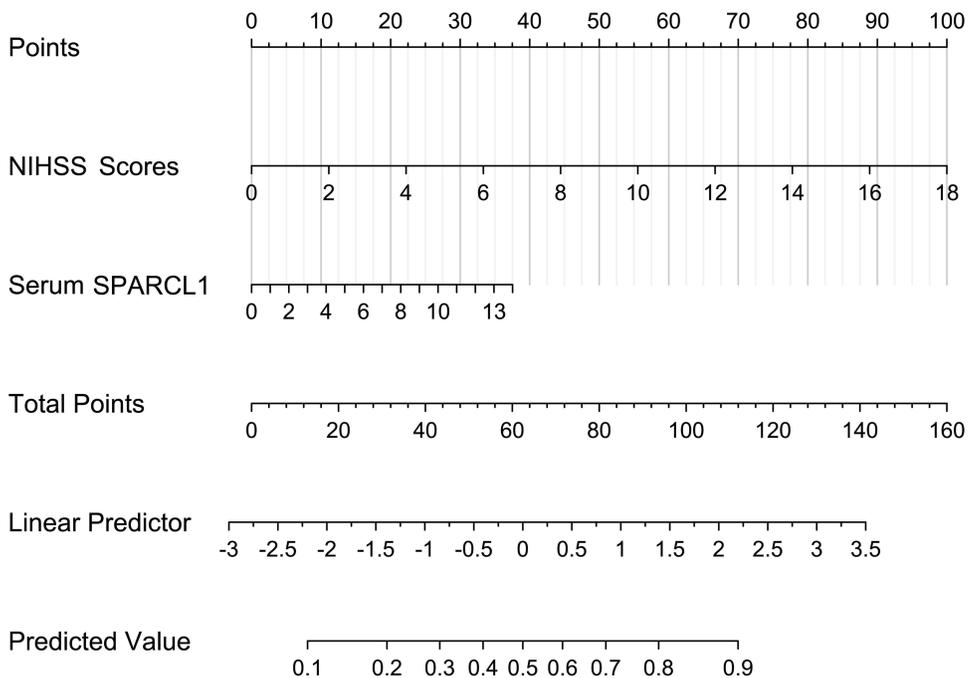


Figure 11 Nomogram predicting the development of early neurologic deterioration following acute intracerebral hemorrhage. Serum secreted protein acidic and rich in cysteine-like I and National Institutes of Health Stroke Scale scores were integrated to predict the development of early neurologic deterioration following acute intracerebral hemorrhage.

Abbreviations: SPARCLI, secreted protein acidic and rich in cysteine-like I; NIHSS, National Institutes of Health Stroke Scale; END, early neurologic deterioration.

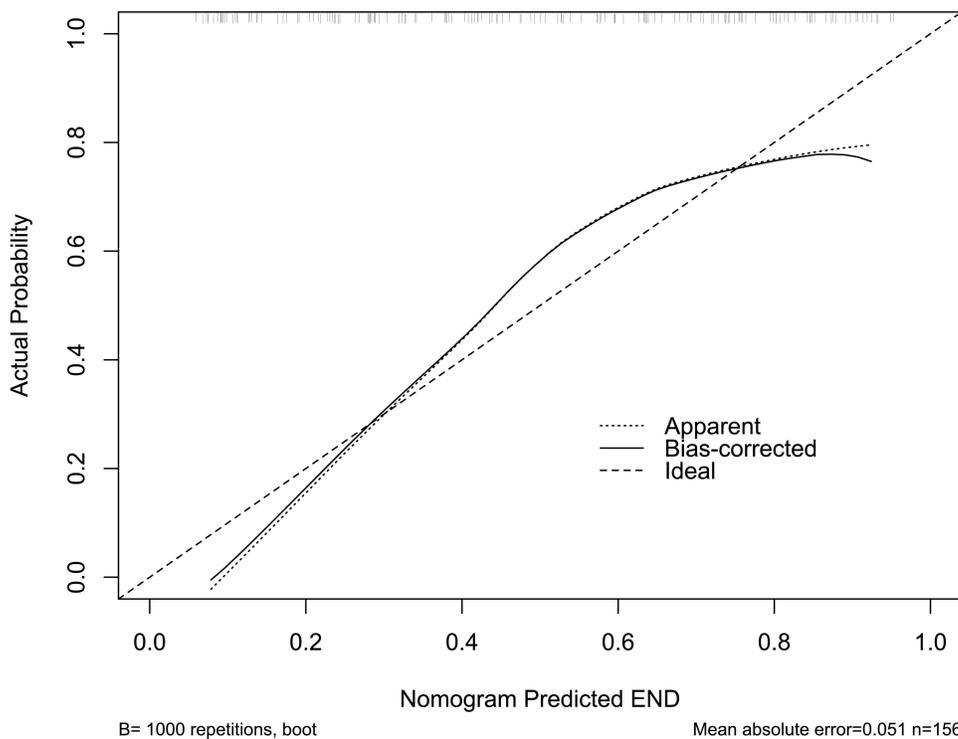


Figure 12 Calibration curve verifying stability of nomogram for predicting the development of early neurologic deterioration after acute intracerebral hemorrhage. The constructed model was of comparative stability for predicting the development of early neurologic deterioration.

Abbreviation: END, early neurologic deterioration.

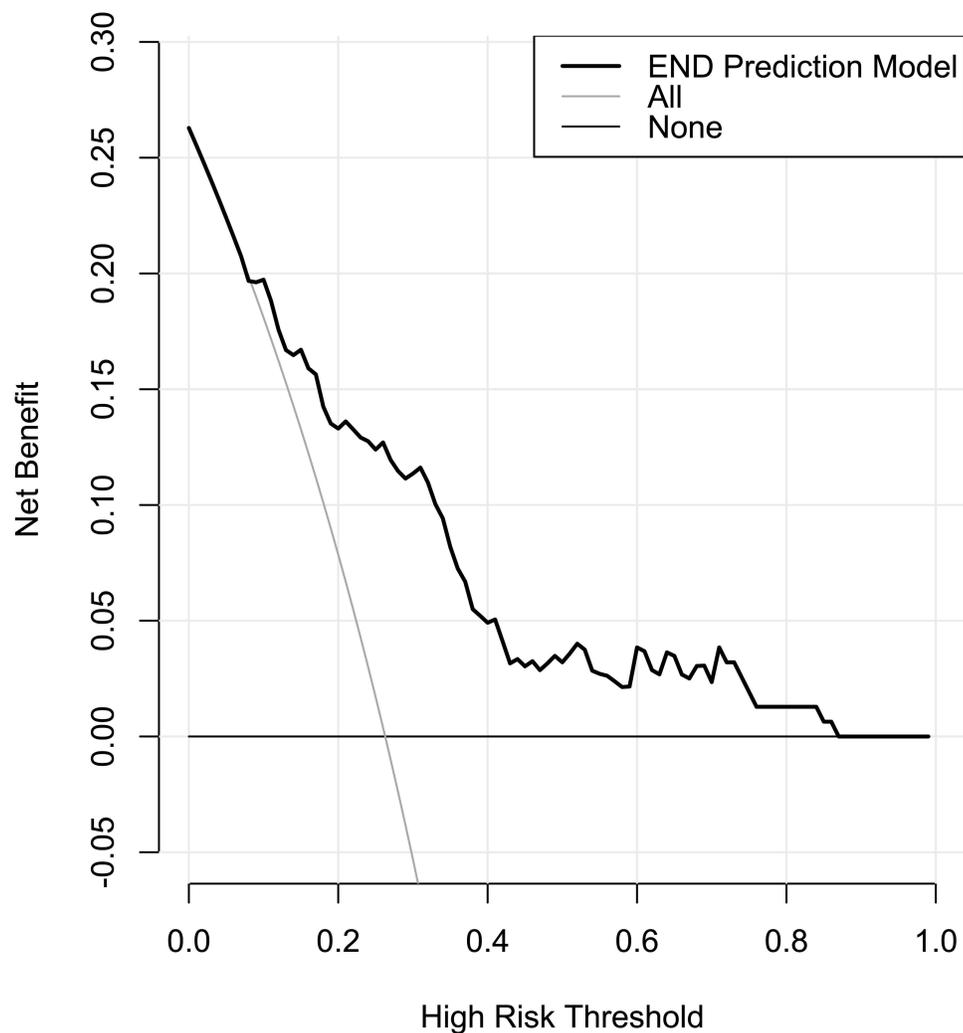


Figure 13 Decision curve validating clinical usability of nomogram in discriminating the development of early neurologic deterioration after acute intracerebral hemorrhage. The configured model was of relative efficiency in the prediction of early neurologic deterioration in clinical work of acute intracerebral hemorrhage.

Abbreviation: END, early neurologic deterioration.

could be guaranteed, and therefore the conclusions may be more scientific and reliable. Three weaknesses are mentioned. (1) only 14 cases had mRS score 6 in this cohort, denoting that 14 patients were deceased within poststroke six months. Owing to a small sample size, a statistical analysis is not performed for investigating relationship between serum SPARCL1 levels and mortality after ICH. Nevertheless, Figure 2 shows that serum SPARCL1 levels were significantly correlated with mRS scores. In other words, serum SPARCL1 levels may be higher in the death than in the alive. However, although we have demonstrated that serum SPARCL1 may be a potential biomarker of ICH, it is interesting if association of serum SPARCL1 levels with mortality will be verified in a large cohort study, in which enough dead patients could be included. (2) There is a subgroup of ICH, which is characterized by a small size of the lesion and manifests clinically as a lacunar syndrome, named as hemorrhagic lacunar stroke.³³ This subgroup, which is usually free of in-hospital death and clinical symptom at discharge in 22.8% of cases, accounts for 7.4% of all ICH cases and is associated with a more favorable prognosis as compared to the remaining group.³³ Because all patients with ICH were admitted at emergency center in this study, such a subgroup of patients were not found and thereof not included for an investigational study. However, a further study of such a subgroup for determining prognostic associations with serum SPARCL1 levels may be informative and clinically valuable in ICH research. (3) although close relation of serum SPARCL1 levels to stroke severity and prognosis following ICH has been confirmed in the current study, the comparisons of prognostic ability between serum SPARCL1 and other biomarkers, such as serum copeptin, C-reactive protein and S100B, may be warranted in future clinical study.

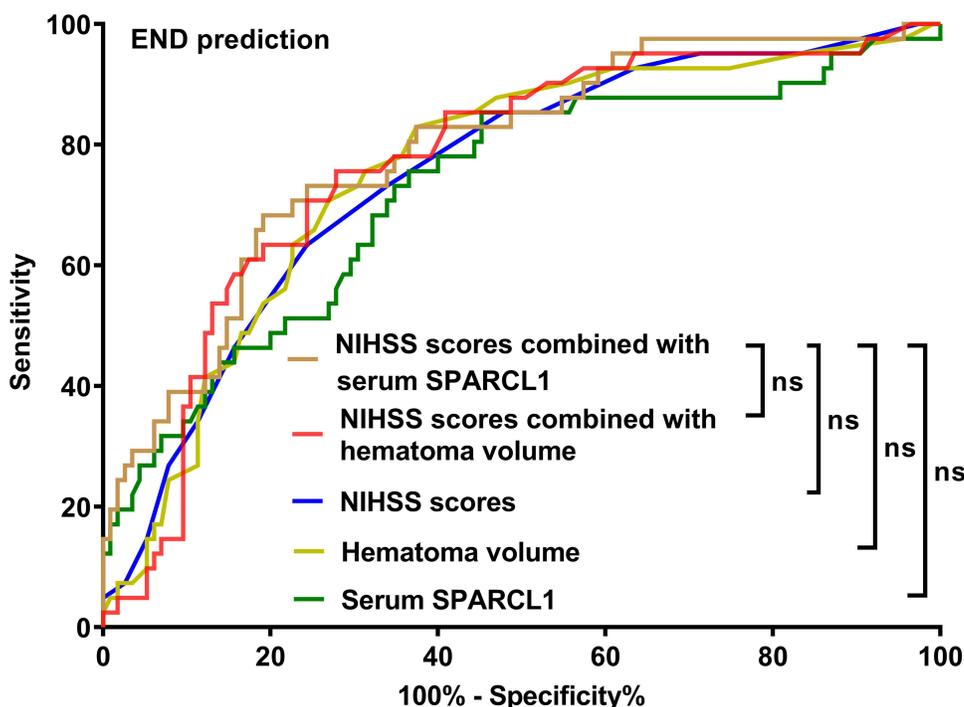


Figure 14 Differences in terms of prediction abilities for the development of early neurologic deterioration between the built prediction model and other variables under the receiver operating characteristic curve. As compared to other variables, including combination of National Institutes of Health Stroke Scale scores with hematoma volume, National Institutes of Health Stroke Scale, hematoma volume and serum secreted protein acidic and rich in cysteine-like I, the prediction model showed insignificantly different area under curve for predicting the development of early neurologic deterioration (all $P > 0.05$).

Abbreviations: SPARCL1, secreted protein acidic and rich in cysteine-like I; NIHSS, National Institutes of Health Stroke Scale; END, early neurologic deterioration; ns, non-significant.

Conclusions

Serum SPARCL1 levels are immediately increased during the early period after ICH, with persistent higher levels at least until day 10. Its admission levels, in independent correlation with NIHSS scores and hematoma volume, were associated with END and poststroke six-month poor prognosis. Also, the prediction model, in which serum SPARCL1, NIHSS scores and hematoma volume were integrated, displayed a significantly strong discriminatory efficiency for poor prognosis. Thus, it is hypothesized that SPARCL1, as a potential serological biomarker, may be of clinical benefit in prognosticating clinical outcome following acute ICH.

Ethics Approval and Consent to Participate

The current study complied with the guidelines of the Declaration of Helsinki and its amendments. Its protocol was endorsed by the Ethics Committee at the First People's Hospital of Fuyang District of Hangzhou City (No. FYD2019011). Signed informed consent forms were acquired from the patients' next of kins or controls themselves.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available because they are personal data but are available from the corresponding author upon reasonable request.

Acknowledgments

We gratefully thank all study participants, their relatives, and the staff at the recruitment centers for their invaluable contributions.

Funding

This research was financially supported by the Hangzhou Science and Technology Plan Project (No. 202107071 918000249496).

Disclosure

The authors declared no potential conflicts of interest in this work.

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