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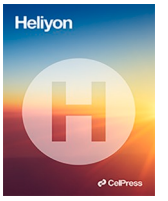

Research article

Usability of serum AIM2 as a predictive biomarker of stroke-associated pneumonia and poor prognosis after acute supratentorial intracerebral hemorrhage: A prospective longitudinal cohort study

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ABSTRACT

Background: Absent in melanoma 2 (AIM2) is implicated in inflammatory processes. We measured serum AIM2 with intent to unveil its predictive significance for stroke-associated pneumonia (SAP) and functional prognosis following acute intracerebral hemorrhage (ICH).

Methods: In this prospective cohort study, serum AIM2 concentrations of 163 ICH patients were gauged upon admission and 57 of them also consented for measurements at days 1, 3, 5, 7, 10 and 14. Coupled with 57 individuals without health conditions, dynamic change of serum AIM2 levels were uncovered. National Institutes of Health Stroke Scale (NIHSS) scores and hematoma volume were identified as the dual indicators of severity. Poststroke six-month modified Rankin Scale (mRS) scores ranging from 3 to 6 indicated an unfavorable outcome. SAP was observed during the first seven days after ICH. Sequential univariate and multivariate analyses were performed to discern predictors of SAP and adverse prognosis.

Results: The serum levels of AIM2 in patients exhibited a marked elevation upon admission, reaching peak levels on the third and fifth days, and remained notably elevated until day 14 compared to those of the control group. Serum AIM2 levels showed independent correlations with both NIHSS scores and the volume of hematoma. Additionally, AIM2 concentrations were independently associated with a poor prognosis and SAP at the six-month mark. Within the framework of restricted cubic spline analysis, serum AIM2 concentrations exhibited a linear correlation with the likelihood of developing SAP and experiencing a poor prognosis. In the context of receiver operating characteristic (ROC) curve analysis, serum AIM2 concentrations effectively differentiated risks of SAP and poor prognosis. By employing segmented analysis, serum AIM2 concentrations showed negligible interactions with several traditional variables, such as age, gender, smoking habits, alcohol consumption, and more. The integrated model incorporating serum AIM2, NIHSS scores, and the volume of hematoma was depicted by employing a nomogram and demonstrated strong predictive performance for poor prognosis or SAP across various evaluation metrics, including ROC curve analysis, calibration curve analysis, and decision curve analysis.

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Conclusion: Serum AIM2 levels show a marked increase shortly after intracerebral hemorrhage (ICH), which may accurately reflect stroke severity, and effectively predict SAP and poor neurological outcomes, and therefore serum AIM2 stands out as an encouraging predictive indicator for ICH.

1. Introduction

Spontaneous intracerebral hemorrhage (ICH), a least treatable type of cerebrovascular disease characterized by a high mortality, is among the primary contributors to global disability burden [1]. Hemorrhagic brain injury involves intricate mechanisms, comprising a sequence of molecular cascades such as inflammatory reaction, oxidative stress, cellular apoptosis, and so on [2]. Undoubtedly, stroke-associated pneumonia (SAP), one of the commonest complications after ICH, greatly worsens clinical outcome of patients [3]. While numerous factors have been acknowledged as predictors of SAP and adverse prognosis following ICH, illness severity, which is very frequently evaluated by employing the National Institutes of Health Stroke Scale (NIHSS) and hematoma volume, is believably accepted to be associated with the risk of SAP and poor prognosis of ICH [4–7]. Noteworthily, neurological researches have focused on exploration of some reliable biomarkers, which may assist in gauging the severity and forecasting the outcome of ICH [8–10].

Inflammasomes are identified as complexes, which are comprised of multiple proteins of involvement in pattern recognition receptors [11–13]. Inflammasome signaling activation leads to the synthesis of active interleukin-1beta and interleukin-18, induces pyroptosis, and therefore participates in pathophysiological processes of numerous illnesses, such as sepsis, stroke, pneumonia and acute myocardial infarction [14–16]. Absent in melanoma 2 (AIM2) is a receptor of cytosolic innate immune [17]. AIM2 inflammasome activation may increase neuroinflammation, damage cerebrovascular integrity, induce cerebral edema, and consequent exacerbation of cognitive performance in animals with acute brain injury [18–20]. Using univariate analysis, increased concentrations of plasma AIM2 were associated with initial NIHSS scores, the extent of cerebral infarction, and 90-day modified Rankin Scale (mRS) scores following acute ischemic stroke in human subjects [21]. Hypothetically, serum AIM2 levels could serve as a promising indicator of sudden cerebral trauma. Here, serum AIM2 concentrations were measured in a group of patients with ICH, followed by an evaluation of its prognostic significance for both SAP and unfavorable functional outcome.

2. Materials and methods

2.1. Study design and ethical considerations

This study was a single-site observational analytical investigation conducted at the Quzhou Affiliated Hospital of Wenzhou Medical University from May 2019 to December 2022. This investigation was assigned into two sub-studies. One segment constituted a cross-sectional analysis aimed at revealing the temporal evolution of serum AIM2 levels following ICH. Here, serum AIM2 concentrations were measured upon admission and during the post-stroke period on days 1, 3, 5, 7, 10 and 14 in patients with ICH who consented for multiple-time-point blood collections. Moreover, serum AIM2 levels were measured in healthy controls upon their enrollment in the study. The second part entailed a prospective cohort investigation aimed at determining whether initial serum AIM2 levels were autonomously linked to the likelihood of developing SAP and experiencing unfavorable outcomes six months following ICH. The research adhered to the guidelines set forth in the Declaration of Helsinki and its subsequent updates. The study protocol received approval from the Ethics Committee at the Quzhou Affiliated Hospital of Wenzhou Medical University (opinion number: LW2021-004). Consent forms were signed either by the patients' legal guardians or by the controls independently.

2.2. Participant recruitments

ICH was diagnosed using head computerized tomography (CT) scan and all ICH patients were consecutively enrolled. The enrollment criteria were as outlined below: (1) participants aged 18 years or older; (2) first-ever stroke; (3) hemorrhagic location in supratentorial space; (4) brain bleeding as a result of primary cause; (5) conservative management of intracerebral hematoma; and (6) hospital admission within the initial 24 h following stroke. There were exclusion requirements in the following: (1) other neurological illnesses, e.g., cerebral infarction, transient ischemia attack, intracranial tumors and central nervous system infections; (2) serious conditions affecting other organs, including malignancies, cardiac insufficiency, renal failure, cirrhosis and ascites; and (3) certain particular conditions, including lung infection preceding stroke onset, need for mechanical ventilation, pregnancies, loss of participants to follow-up, inadequate data, reluctance to participate, and samples not meeting the required standards. The control group consisted of individuals who were healthy volunteers. They did not have certain chronic conditions, such as hypertension, diabetes mellitus and hyperuricemia. Certain traditional diagnostic tests yielded values within acceptable parameters, including blood leucocyte count, blood neutrophil count, blood sugar level and blood electrolyte levels.

2.3. Data collection

When patients entered into emergency room, we inquired about (1) conventional demographical information, such as age and gender; (2) certain factors that increase the risk of vascular problems, including smoking tobacco, consuming alcohol, having high

blood pressure, diabetes, experiencing abnormal lipid levels, chronic obstructive pulmonary disease, ischemic heart disease and hyperuricemia; and (3) some specific medications, such as statins, blood-thinning drugs, and medications that prevent blood clotting and therefore are often prescribed to manage vascular conditions. Also, time of arrival and blood-collection time after stroke were registered. Systolic and diastolic blood pressure readings were obtained using a non-invasive method. Using the swallow test, dysphasia was assessed. Vomiting was observed and then recorded. Radiological parameters, which were identified using head CT scans, included the volume of hematoma (which was determined with formula $0.5 \times a \times b \times c$ [22]), bleeding sites (superficial and deep), expansion of blood clot into the brain's ventricular system and expansion of blood clot into the space surrounding the brain. The NIHSS at admission was chosen as a clinical indicator of the severity of ICH [23]. Following the guidelines outlined by the consensus group on SAP, SAP was characterized by the occurrence of infections affecting the lower airways within the initial 7 days following the onset of stroke [24]. By utilizing mRS, neurological function status was assessed at poststroke six-month and scores ranging from 3 to 6 indicated an unfavorable prognosis [25].

2.4. Immune analysis

According to the voluntary compliance principle, admission venous blood could be drawn from all patients, while on post-stroke days 1, 3, 5, 7, 10 and 14, blood samples were obtained only from a subset of patients. Samples of blood from the control group were acquired at their enrollments into our study. All participants underwent venipuncture in the antecubital area to extract 5 mL of blood, which was promptly deposited into a biochemistry tube pre-filled with gel. Once coagulation occurred, blood samples were subjected to centrifugation at 2000*g* for a duration of 10 min. Then, the liquid portion above the sediment in isolation were transferred into Eppendorf tubes and were promptly stored in a freezer at a temperature of −80 °C for subsequent analysis. Every quarter, a group of serum samples was thawed for the detection of serum AIM2 using ELISA. The kit was produced from Shanghai Bolsen Biotechnology Co., Ltd (Item No. BES3068K). The range of detection spanned from 0.156 to 10 ng/ml, with intra-assay variability below 10 % and

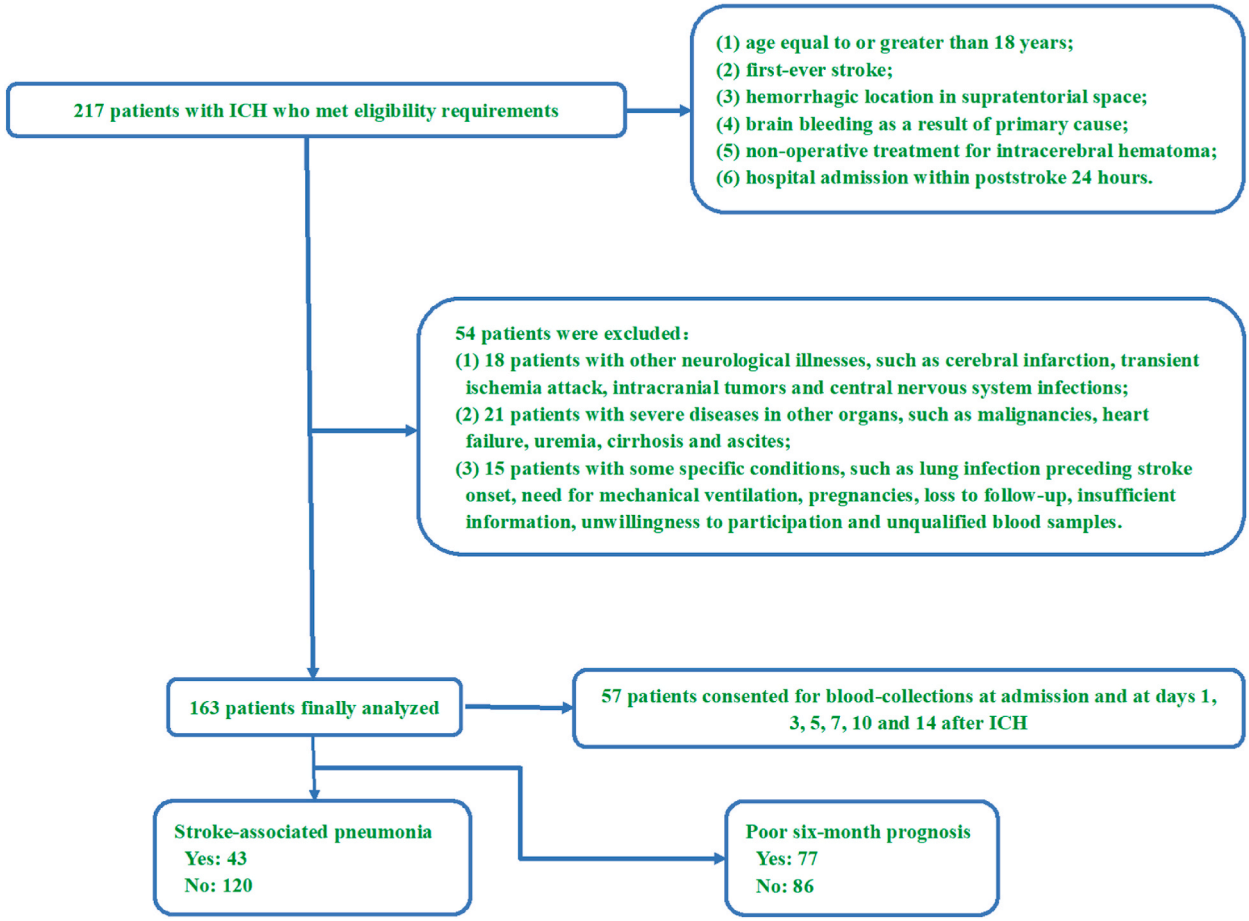

Fig. 1. Flowchart depicting the selection process for eligible patients with acute intracerebral hemorrhage. A group of consecutively enrolled 217 individuals with acute intracerebral hemorrhage were assessed, leading to a final group of 163 participants chosen for clinical examination. From this pool, 57 patients agreed with multiple-time-point blood-drawings, 43 had development of stroke-associated pneumonia and 77 suffered from adverse outcomes six months post the onset of stroke. ICH indicates intracerebral hemorrhage.

inter-assay variability likewise below 10 %. All quantifications were conducted twice by the same proficient personnel unaware of clinical details. The outcomes of two measurements were combined for statistical evaluation.

2.5. Statistical analysis

Data were analyzed with the SPSS program (version 23.0; SPSS Inc., Chicago, IL, USA). Categorical variables were presented as frequencies (percentages), and intergroup comparisons were conducted by employing the chi-square test or Fisher's exact test when applicable. The Kolmogorov–Smirnov assessment was utilized for determining normal distribution of quantitative variables. Based on patterns of data distribution, numerical parameters were reported as either mean (with standard deviation, SD) or median (with interquartile range, IQR), and distinctions between groups were evaluated by employing the independent-sample Student's t-test or Mann-Whitney *U* test, as deemed suitable. Using the Friedman's test, the temporal trajectory of serum AIM2 concentrations following ICH was assessed. To explore autonomous predictors of SAP and unfavorable prognosis at six months, two separate binary multivariable logistic regression models were formulated. These models included SAP and six-month poor prognosis as the respective dependent variables, and significant variables identified through univariate analyses were integrated. Also, subgroup analysis and interaction were done among serum AIM2 levels and several conventional variables in the prediction of SAP and unfavorable prognosis at six months post-ICH. To identify variables that exhibited independent associations with serum AIM2 levels, significant variables determined by the Spearman test were included in a multivariate linear regression model for subsequent statistical examination. The ROC curve analysis was conducted using MedCalc 20 (MedCalc Software, Ltd, Ostend, Belgium) to assess discriminatory performance, with areas under the ROC curve (AUCs) utilized as measures of discrimination. The optimal cutoff value for serum AIM2 concentrations was determined by employing the Youden approach. Subsequently, in R 3.5.1 software, graphical representations including restricted cubic splines, nomograms, calibration curves, and decision curves were generated. ROC curves were generated using GraphPad Prism 7.01 (GraphPad Software Inc., San Diego, California, USA). The sample size was determined using MedCalc 20. In sample size module, whether in correlation analysis, comparison of two groups, ROC curve analysis or others, a collective of 163 patients was deemed adequate for clinical scrutiny in this investigation. Variances with a two-tailed P value below 0.05 were regarded as statistically noteworthy.

3. Results

3.1. Study populations and characteristics

In Fig. 1, a consecutive enrollment of 217 patients with ICH was finished in accordance with the prespecified eligibility requirements, afterwards fifty-four patients were eliminated and lastly, a cumulative of 163 patients were included for subsequent epidemiological study. Within this cohort, 43 experienced SAP, 77 suffered from poor six-month prognosis and 57 individuals consented to blood collection at various specified intervals following ICH.

To investigate the longitudinal alterations in serum AIM2 levels, 57 healthy controls were enrolled, comprising 31 males and 26 females. The age spanned from 40 to 88 years within this group (median, 62 years; percentiles 25th-75th, 55–71 years). Also, 24 individuals were smokers, and 22 were consumers of alcohol. As for that group of cases containing 57 individuals, there were 29 men and 28 women, with ages ranging from 43 to 84 years (median, 66 years; percentiles 25th-75th, 55–72 years). In total, 20 patients smoked and 22 drank. Clearly, statistically significant disparities were evidently absent in the median age and proportions of males, smokers, and drinkers among the group of patients and the comparison cohort (All P-values were greater than 0.05.).

All 163 patients were comprised of 93 males and 70 females. The participants' ages spanned from 42 to 85 years, with an average age of 61.9 years and a standard deviation of 11.0 years. A total of 78 patients were aged at 65 or greater years. Among the participants, 63 individuals reported smoking cigarettes, 70 reported consuming alcohol, 105 diagnosed with hypertension, 36 diabetic subjects, 57 dyslipidemic suffers, 6 cases with chronic obstructive pulmonary disease, 9 individuals with ischemic heart disease and 9 hyperuricemic patients. The prescribed medications consisted of statins for 47 individuals, anticoagulants for 11 patients, and antiplatelet agents for 23 participants. After ICH, the duration of hospital admission ranged from 1 to 24 h, with a median of 8 h and percentiles ranging from 5 to 14 h. Blood collection time ranged from 2 to 25 h, with a median of 9 h and percentiles ranging from 6 to 15 h. Thirty-two patients suffered from dysphasia and 35 experienced vomiting. The range of blood pressure during heart contraction extended from 109 to 212 mmHg, with a mean of 145.9 mmHg and a SD of 23.4 mmHg. blood pressure during heart relaxation ranged from 67 to 111 mmHg, with a mean of 85.2 mmHg and a SD of 9.7 mmHg. Superficial hematomas were present in 50 patients, whereas deep hematomas were observed in 113 patients. Expansion of the blood clot into the brain's ventricular system was observed in 33 individuals, while subarachnoid extension occurred in 16 patients. The NIHSS demonstrated a spectrum of values from 0 to 18, with a median score of 11 and quartiles ranging from 7 to 13. Hematoma volume exhibited variability spanning from 2 to 36 mL, with a median volume of 10 mL and quartiles ranging from 8 to 17 mL. An aggregate of 43 patients had the development of SAP and poststroke six-month mRS scores ranged from 0 to 6, with a middle score of 2 and quartiles ranging from 2 to 4. The scores ranged from 0 to 6 were found in 11, 26, 49, 27, 24, 12 and 14 patients respectively. Altogether, 77 patients presented with a poor prognosis.

3.2. Serum AIM2 levels and ICH severity

As depicted in Fig. 2, serum AIM2 concentrations in patients exhibited a notable elevation upon admission, followed by a subsequent rise, peaking by the third and fifth days, before steadily declining by day 14 post-ICH. Additionally, AIM2 levels at all time

points showed notable increases in contrast to those of the control group ($P < 0.001$). As demonstrated in Table 1, serum AIM2 concentrations displayed close associations with diabetes, expansion of the blood clot into the brain's ventricular cavities, NIHSS scores, the volume of hematoma, white blood cell count, and blood glucose levels (all P-values less than 0.05). Upon incorporation of each aforementioned significant variable in the multivariate linear regression model, only NIHSS scores (beta, 0.396; 95 % CI, 0.212–0.581; VIF, 2.469; $P = 0.001$) and the volume of hematoma volume (beta, 0.112; 95 % CI, 0.003–0.221; VIF, 2.744; $P = 0.045$) exhibited independent associations with serum AIM2 concentrations.

3.3. Serum AIM2 concentration and poor neurological function outcome

As illustrated in Fig. 3, serum AIM2 concentrations exhibited a significant elevation corresponding to escalating mRS scores from 0 to 6 ($P < 0.001$). Furthermore, a strong positive correlation emerged between serum AIM2 concentrations and mRS scores (P-value was less than 0.001; Fig. 4). Subjects with unfavorable outcomes, in contrast to those with favorable outcomes, had substantially higher percentages of age≥65 years, dysphasia and intraventricular extension of hematoma, as well as displayed significantly elevated NIHSS scores, increased volume of hematoma, elevated blood glucose levels and heightened serum AIM2 concentrations (All P-values were less than 0.05; Table 2). In Fig. 5, serum AIM2 concentrations exhibited a linear correlation with the likelihood of unfavorable outcomes ($P > 0.05$). And in Fig. 6, the levels efficiently distinguished such a risk ($P < 0.001$). All significant variables mentioned earlier were included in the categorical logistic regression model, revealing that NIHSS scores (OR, 1.304; 95 % CI, 1.112–1.535; $P = 0.001$), the volume of hematoma (OR, 1.066; 95 % CI, 1.004–1.133; $P = 0.015$) and serum AIM2 concentrations (OR, 1.165; 95 % CI, 1.030–1.318; $P = 0.037$) emerged as independent predictors of unfavorable outcomes (Hosmer-Lemeshow goodness-of-fit test, $P > 0.05$). Using subgroup analysis and interaction analysis, serum AIM2 levels non-statistically significantly interacted with additional variables including age, gender, hypertension, etc. (all $P > 0.05$; Table 3). The three independent factors associated with unfavorable prognosis were consolidated into a comprehensive model, illustrated through a nomogram presentation (Fig. 7). The calibration curve analysis indicated that the model exhibited robust stability (Fig. 8). The decision curve analysis demonstrated that the model was clinically fit (Fig. 9). It is noteworthy that serum AIM2 displayed comparable AUC values in comparison to NIHSS scores and the volume of hematoma (both P-values were greater than 0.05.). Additionally, the model demonstrated enhanced predictive efficacy in terms of AUC when compared to serum AIM2, NIHSS scores, the volume of hematoma, and their combined utilization (All P-values were less than 0.05; Fig. 10).

3.4. Serum AIM2 levels and SAP risk

As delineated in Table 4, patients with development of SAP, in contrast to those without, exhibited markedly higher proportions of dysphasia and vomiting, as well as had significantly elevated NIHSS scores, increased volume of hematoma, elevated blood glucose levels, and higher serum AIM2 concentrations (all with P-values less than 0.05). As depicted in Fig. 11, a strong linear association was noted between serum AIM2 concentrations and the risk of SAP (P-value exceeded 0.05). Moreover, serum AIM2 concentrations effectively differentiated patients susceptible to SAP ($P < 0.001$; Fig. 12). The significant variables aforementioned were integrated incorporated into the categorical logistic regression model, revealing that NIHSS scores (OR, 1.123; 95 % CI, 1.088–1.400; $P = 0.004$),

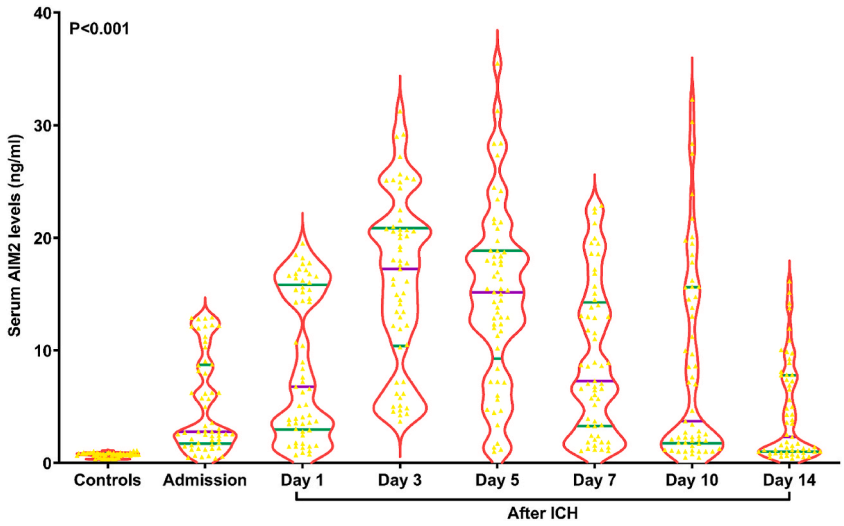

Fig. 2. Longitudinal change of serum absent in melanoma 2 levels subsequent to acute intracerebral hemorrhage. Patients afflicted by acute intracerebral hemorrhage, in contrast to individuals without any known neurological disorders, displayed substantially rising serum absent in melanoma 2 levels during fourteen days after stroke. The levels peaked on day 3 and plateaued on day 5 following the onset of stroke ($P < 0.001$). ICH stands for intracerebral hemorrhage; AIM2, absent in melanoma 2.

Table 1
Factors in correlation with serum absent in melanoma 2 levels after acute intracerebral hemorrhage.

Components	ρ	P value
Age ≥65 years	−0.088	0.264
Gender (male/female)	−0.125	0.112
Cigarette consumption	−0.006	0.941
Alcohol consumption	−0.113	0.150
Hypertension	0.043	0.585
Diabetes mellitus	0.194	0.013
Dyslipidemia	0.094	0.235
COPD	0.101	0.199
Ischemic heart ischemic	0.079	0.318
Hyperuricemia	0.045	0.565
Previous statin use	−0.011	0.890
Previous anticoagulant use	0.107	0.174
Previous antiplatelet use	0.073	0.354
Hospital admission time (h)	−0.054	0.495
Blood sampling time (h)	−0.048	0.547
Dysphasia	0.090	0.255
Vomiting	0.088	0.266
Systolic arterial pressure (mmHg)	−0.114	0.148
Diastolic arterial pressure (mmHg)	0.008	0.916
Hemorrhagic locations (superficial/deep)	−0.039	0.618
Intraventricular extension of hematoma	0.174	0.026
Subarachnoidal extension of hematoma	0.112	0.154
NIHSS scores	0.574	<0.001
Hematoma volume (ml)	0.596	<0.001
Blood leucocyte count ($\times 10^9$/l)	0.170	0.030
Blood glucose levels (mmol/l)	0.192	0.014

Correlations were reported as ρ values using the Spearman test. NIHSS means National Institutes of Health Stroke Scale; COPD, chronic obstructive pulmonary disease.

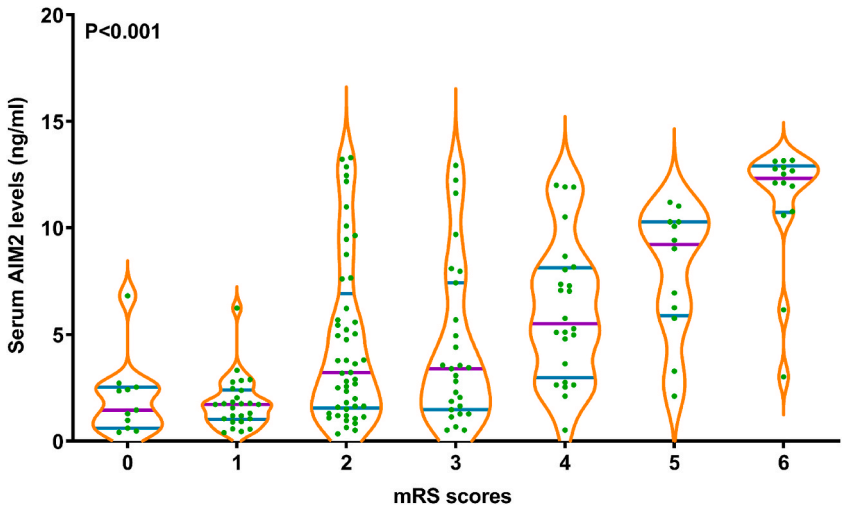

Fig. 3. Serum absent in melanoma 2 in relation to modified Rankin Scale scores at six months post-acute intracerebral hemorrhage. Serum absent in melanoma 2 concentrations were markedly reduced in individuals with a Modified Rankin Scale score of 0 at six months, progressively increasing across scores 1 to 5, and peaking among those with a score of 6 ($P < 0.001$). mRS indicates modified Rankin Scale; AIM2, absent in melanoma 2.

hematoma volume (OR, 1.103; 95 % CI, 1.043–1.167; P = 0.018), and serum AIM2 concentrations (OR, 1.109; 95 % CI, 1.002–1.227; P = 0.047) showed autonomous associations with SAP risk. As illustrated in Table 5, there were no notable interactions observed between serum AIM2 concentrations and additional factors, encompassing age, gender, hypertension, and so forth (All P-values surpassed 0.05). The preceding autonomous factors (namely, serum AIM2, NIHSS scores and the volume of hematoma) was incorporated to formulate a composite model, which was exhibited using a nomogram (Fig. 13). The model demonstrated relative stability in the calibration curve assessment (Fig. 14) and showed medical effectiveness in the decision graph assessment (Fig. 15). As depicted in Fig. 16, despite the AUC of serum AIM2 was comparable to that of NIHSS scores and the volume of hematoma (both with P-values greater than 0.05), the model did not demonstrate markedly stronger forecasting performance relative to other factors, such as hematoma volume, NIHSS scores, and their amalgamation (all with P-values exceeding 0.05).

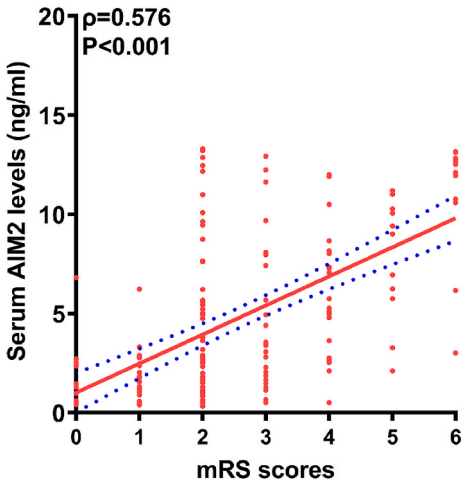

Fig. 4. Serum absent in melanoma 2 levels and modified Rankin Scale scores at six months post-acute intracerebral hemorrhage. Serum absent in melanoma 2 levels exhibited a strong correlation with six months modified Rankin Scale scores following stroke ($P < 0.001$). mRS indicates modified Rankin Scale; AIM2, absent in melanoma 2.

Table 2
Factors related to six-month poor prognosis after acute intracerebral hemorrhage.

Components	mRS 3-6	mRS 0-2	P value
Age ≥65 years	45 (58.4 %)	33 (38.4 %)	0.010
Gender (male/female)	40/37	53/33	0.213
Cigarette consumption	28 (36.4 %)	35 (40.7 %)	0.571
Alcohol consumption	28 (36.4 %)	42 (48.8 %)	0.108
Hypertension	49 (63.6 %)	56 (65.1 %)	0.844
Diabetes mellitus	19 (24.7 %)	17 (19.8 %)	0.451
Dyslipidemia	31 (40.3 %)	26 (30.2 %)	0.180
COPD	5 (6.5 %)	1 (1.2 %)	0.101
Ischemic heart ischemic	6 (7.8 %)	3 (3.5 %)	0.309
Hyperuricemia	7 (9.1 %)	2 (2.3 %)	0.059
Previous statin use	24 (31.2 %)	23 (26.7 %)	0.534
Previous anticoagulant use	6 (7.8 %)	5 (5.8 %)	0.615
Previous antiplatelet use	9 (11.7 %)	14 (16.3 %)	0.401
Hospital admission time (h)	8 (5–12)	9 (5–16)	0.157
Blood sampling time (h)	9 (6–13)	10 (6–17)	0.179
Dysphasia	21 (27.3 %)	11 (12.8 %)	0.020
Vomiting	20 (26.0 %)	15 (17.4 %)	0.185
Systolic arterial pressure (mmHg)	144.8 ± 23.5	146.9 ± 23.4	0.578
Diastolic arterial pressure (mmHg)	85.4 ± 10.6	85.0 ± 8.9	0.824
Hemorrhagic locations (superficial/deep)	25/52	25/61	0.639
Intraventricular extension of hematoma	21 (27.3 %)	12 (14.0 %)	0.035
Subarachnoidal extension of hematoma	10 (13.0 %)	6 (7.0 %)	0.198
NIHSS scores	13 (11–15)	8 (6–11)	<0.001
Hematoma volume (ml)	15 (10–19)	8 (5–10)	<0.001
Blood leucocyte count (× 10^9/l)	7.4 (4.9–9.1)	6.8 (5.5–8.7)	0.917
Blood glucose levels (mmol/l)	9.7 (7.6–14.9)	9.0 (7.7–10.8)	0.040
Serum AIM2 levels (ng/ml)	6.3 (3.0–10.6)	2.4 (1.2–4.8)	<0.001

Variables were summarized in form of count (percentage), mean ± standard deviation or median (upper-lower quartiles). The Chi-square test, Fisher exact test, Student's *t*-test or Mann-Whitney test was in utilization for data comparisons. NIHSS indicates National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; COPD, chronic obstructive pulmonary disease; AIM2, absent in melanoma 2.

4. Discussion

As far as we are aware, it remains uninvestigated whether there are changes in serum AIM2 levels following ICH and whether the levels are pertinent to severity and clinical outcomes of such patients. Within this group of patients diagnosed with ICH, several noteworthy findings were ascertained. First, in comparison to individuals without any health conditions, serum AIM2 levels were immediately elevated at admission of patients and such substantially higher levels persisted until poststroke day 14, with peaking measurements on the third and fifth days. Second, serum AIM2 concentrations in patients showed autonomous correlations with NIHSS scores and the volume of hematoma. Thirdly, serum AIM2 concentrations demonstrated autonomous associations with both

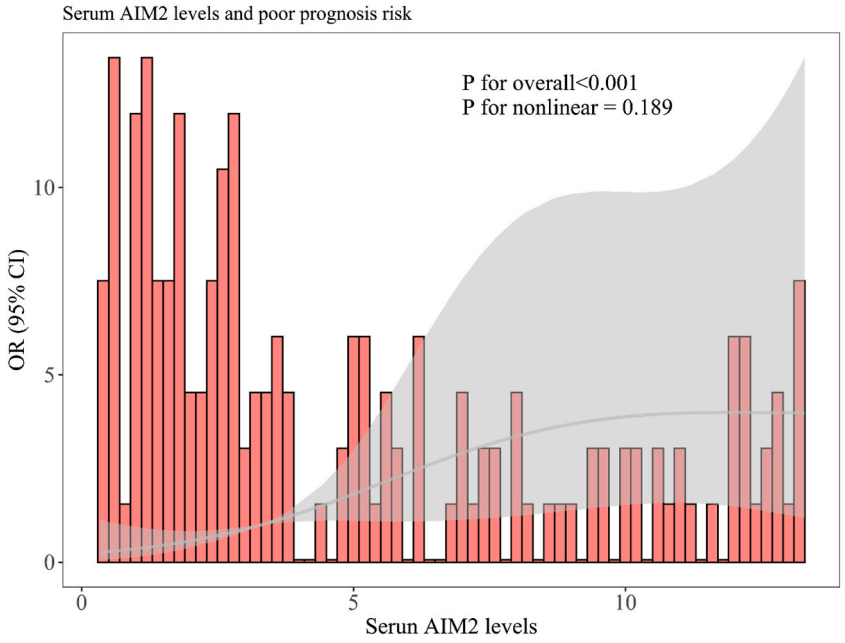

Fig. 5. Restricted cubic spline illustrating the linear association between serum absent in melanoma 2 concentrations and the likelihood of adverse outcomes at six months post-acute intracerebral hemorrhage. Serum absent in melanoma 2 concentrations exhibited a linear correlation with the risk of poor prognosis at six months following stroke. AIM2 denotes absent in melanoma 2; OR, odds ratio; 95 % CI, 95 % confidence interval.

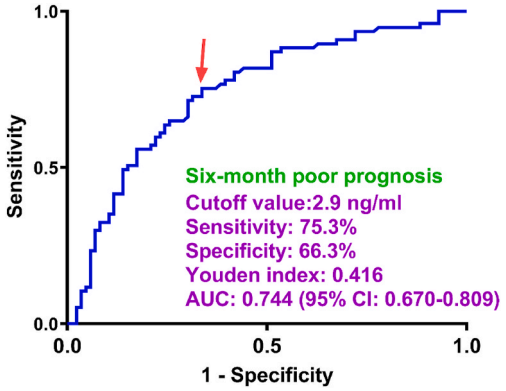

Fig. 6. Predictive capacity for prognosis of serum absent in melanoma 2 levels after acute intracerebral hemorrhage evaluated by receiver operating characteristic curve. Serum absent in melanoma 2 concentrations effectively differentiated the likelihood of adverse outcomes at the six-month mark after hemorrhagic stroke. Employing the Youden approach, the threshold value of serum absent in melanoma 2 concentrations was selected, which anticipated unfavorable prognostic outcomes with the corresponding sensitivity and specificity. AUC means area under curve; 95 % CI, 95 % confidence interval.

SAP and unfavorable outlook at six months post-stroke. Lastly, in comparison to NIHSS scores and the volume of hematoma, serum AIM2 exhibited strong predictive capabilities for identifying both SAP and unfavorable prognosis. However, models integrating serum AIM2, NIHSS scores, and hematoma volume demonstrated satisfactory effectiveness in forecasting unfavorable outcomes at the six-month interval, but were less effective in distinguishing SAP risk. The preceding findings are sufficiently suggestive of the conception that serum AIM may emerge as a prospective indicator for evaluating severity and prognosticating functional status in ICH.

Clearly, AIM2 functions as an inflammatory mediator [26]. It can be detected within central nervous system and its expressions are greatly up-regulated under brain pathological situations comprising ischemic, hemorrhagic and traumatic injuries to the brain [18–20,27,28]. Accumulating data have shown that AIM2 might pose harmful risks in acute brain injury conditions [18–20,27,28]. Specifically, AIM2 inflammasome-triggered pyroptosis was initiated in cerebral microvascular endothelial cells following controlled cortical impact-induced trauma in mice [28]. Consistently, hindering AIM2 inflammasome activation using gene-knocking down technique markedly attenuated pyroptosis during the initial stages of brain injury following hemorrhage into the subarachnoid space [18]. Similarly, AIM2 deletion obviously decreased cerebral infarct size, enhanced neurological and motor functions, and reduced

Table 3
Subgroup analysis and intersubgroup interaction analysis between serum absent in melanoma levels and 6-month poor prognosis after acute intracerebral hemorrhage.

Subgroup analysis		Total (n)	OR (95 % CI)	P value	$P_{interaction}$ value
Age	≥65 years	78	1.255 (1.009–1.560)	0.042	0.362
	<65 years	85	1.142 (0.982–1.329)	0.085	
Gender	Male	93	1.172 (1.002–1.371)	0.047	0.267
	Female	70	1.071 (0.906–1.265)	0.424	
Cigarette consumption	Yes	63	1.173 (0.970–1.418)	0.101	0.419
	No	100	1.142 (1.001–1.302)	0.049	
Alcohol consumption	Yes	70	1.147 (1.002–1.313)	0.046	0.127
	No	93	1.194 (1.008–1.414)	0.040	
Hypertension	Yes	105	1.246 (1.030–1.507)	0.023	0.187
	No	58	1.054 (0.915–1.213)	0.467	
Diabetes mellitus	Yes	36	1.040 (0.769–1.408)	0.797	0.236
	No	127	1.138 (1.007–1.286)	0.039	
Dyslipidemia	Yes	57	0.943 (0.769–1.156)	0.570	0.175
	No	106	1.224 (1.050–1.428)	0.010	
Previous statin use	Yes	47	0.937 (0.751–1.170)	0.568	0.121
	No	116	1.228 (1.065–1.416)	0.005	
Previous antiplatelet use	Yes	23	1.210 (0.861–1.702)	0.272	0.481
	No	140	1.134 (1.002–1.283)	0.046	

Associations were adjusted for age, dysphasia, intraventricular extension of hematoma, National Institutes of Health Stroke Scale scores, hematoma volume and blood glucose levels. OR denotes odds ratio; 95 % CI, 95 % confidence interval.

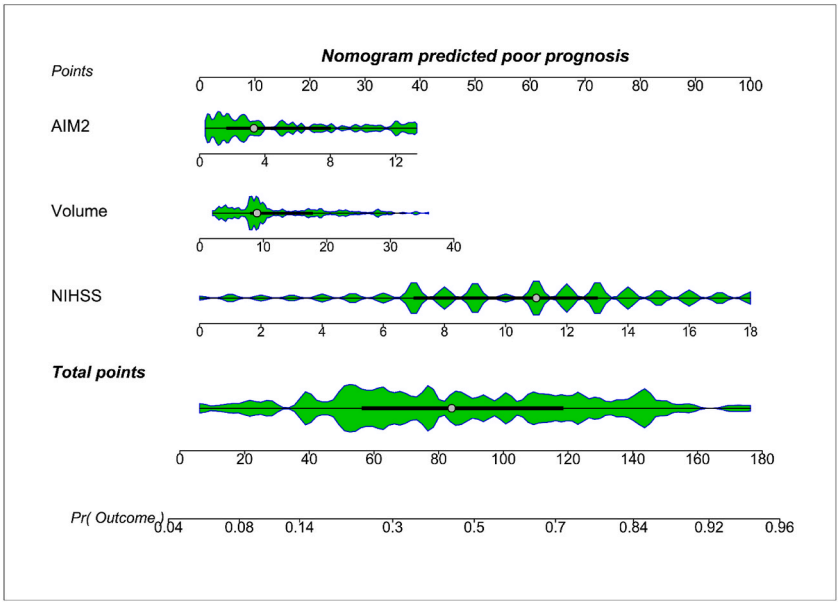

Fig. 7. Nomogram assessing the predictive model for prognosis in individuals with acute intracerebral hemorrhage. Serum absent in melanoma 2, hematoma size and National Institutes of Health Stroke Scale scores were combined to differentiate the likelihood of an unfavorable prognosis six months after acute intracerebral hemorrhage. NIHSS denotes National Institutes of Health Stroke Scale; AIM2, absent in melanoma 2.

blood-brain barrier breakdown after blockage of the middle cerebral artery in mice [20]. Overall, AIM2 could potentially serve as a focus for treating acute brain injury.

Among 85 individuals diagnosed amid sudden ischemic stroke, plasma AIM2 concentrations showed a notable increase, as compared to 85 healthy controls [21]. Our study explored the dynamic fluctuations in serum AIM2 levels following ICH. Our finding is that serum AIM2 levels were obviously raised after ICH, reached its peak at day 3 and remained stable from day 5 and were persistent to keep substantially higher until day 14, in comparison to individuals without any medical conditions. Also, AIM2 levels in cerebrospinal fluid were notably elevated in individuals diagnosed with aneurysmal subarachnoid hemorrhage [18]. In consideration of its production from central nervous system [18–20,27,28], a portion of serum AIM2 might originate from cerebral tissues.

Since a recent univariate analysis showed plasma AIM2 concentrations exhibited strong correlations with NIHSS scores and ischemic stroke volume of patients with acute cerebral infarction [21], as far as we are aware, no research has been done to analyze relationship between circulating AIM2 levels and stroke severity using multivariate analysis. In our study, univariate analysis followed

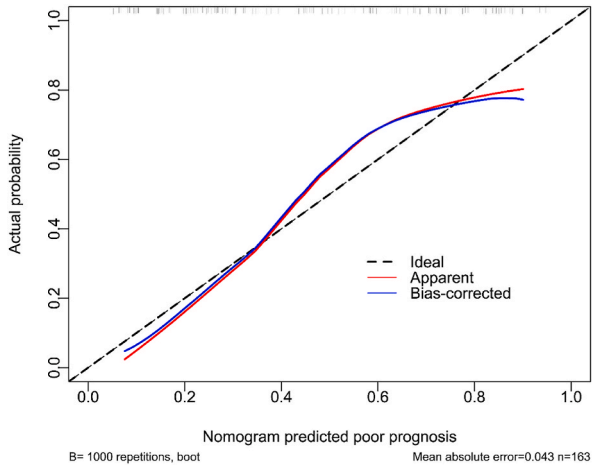

Fig. 8. Calibration plot assessing the reliability of the nomogram in predicting the likelihood of an adverse prognosis six months after stroke. The constructed framework remained consistent in forecasting an unfavorable outcome six months following the onset of acute intracerebral hemorrhage.

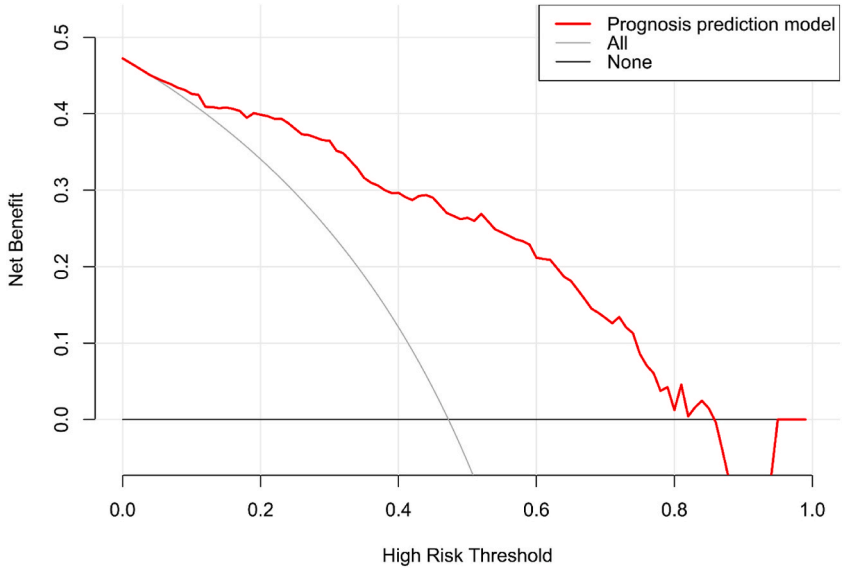

Fig. 9. The decision curve assessed the clinical applicability of the model in identifying the likelihood of an adverse outcome six months after stroke. The developed model demonstrated clinical utility in forecasting adverse outcomes six months following intracerebral hemorrhage.

by multivariate analysis was implemented to demonstrate if serum AIM2 concentrations are autonomously linked to the seriousness of ICH. Our interesting results are that serum AIM2 concentrations actually were autonomous linked to NIHSS scores and the volume of hematoma. Stated differently, serum AIM2 could serve as a promising biological marker to assist in assessing the severity of ICH.

Plasma AIM2 levels have been found to be highly correlated with mRS scores at 90 days after acute cerebral infarction [21]. However, the preceding results were verified using univariate analysis. AIM2 may be involved in lung inflammatory processes of some diseases, such as idiopathic pulmonary fibrosis, streptococcus pneumoniae infection and Pseudomonas aeruginosa infection [29–31]. Also, SAP occurrence is tightly linked to a heightened likelihood of unfavorable outcomes following ICH [32]. SAP was also considered as the prognostic parameter within this group of patients diagnosed with ICH. Using multivariate analysis, serum AIM2 concentrations, alongside NIHSS scores and the volume of hematoma, demonstrated independent associations with SAP and unfavorable outcomes following ICH. In the analysis using restricted cubic splines, a clear linear relationship was observed between serum AIM2 concentrations and the likelihood of both SAP and unfavorable prognosis, suggesting the rationality of employing serum AIM2 as a continuous variable in this investigation. Also, we found non-interactional effects among serum AIM2 concentrations and various factors, including age, sex, hypertension, diabetes mellitus, and others. Taken together, serum AIM2 holds potential as a robust biochemical indicator for forecasting the likelihood of SAP and unfavorable prognostic outcomes six months following ICH.

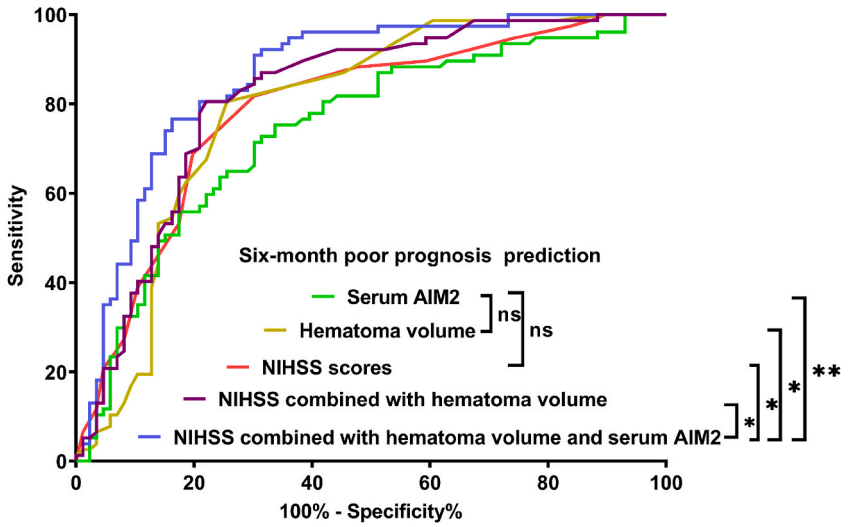

Fig. 10. Receiver operating characteristic curve evaluating prognostic capacity of serum absent in melanoma 2 concentrations and combined model for adverse outcomes six months following acute intracerebral hemorrhage. Serum absent in melanoma 2 levels had similar prognosis predictive ability, as compared to National Institutes of Health Stroke Scale scores and the volume of hematoma. Combination of National Institutes of Health Stroke Scale scores with hematoma volume and serum absent in melanoma 2 showed significantly higher prognosis predictive ability, as opposed to other variables. AIM2 means absent in melanoma 2; NIHSS, National Institutes of Health Stroke Scale; ns, non-significant. *P < 0.05, **P < 0.01.

Table 4
Factors in relation to stroke-associated pneumonia after acute intracerebral hemorrhage.

Components	SAP	Non-SAP	P values
Age ≥65 years	23 (53.5 %)	55 (45.8 %)	0.389
Gender (male/female)	27/16	66/54	0.376
Cigarette consumption	18 (41.9 %)	45 (37.5 %)	0.614
Alcohol consumption	20 (46.5 %)	50 (41.7 %)	0.582
Hypertension	28 (65.1 %)	77 (64.2 %)	0.911
Diabetes mellitus	14 (32.6 %)	22 (18.3 %)	0.054
Dyslipidemia	12 (27.9 %)	45 (37.5 %)	0.258
COPD	2 (4.7 %)	4 (3.3 %)	0.655
Ischemic heart ischemic	1 (2.3 %)	8 (6.7 %)	0.447
Hyperuricemia	1 (2.3 %)	8 (6.7 %)	0.447
Previous statin use	10 (23.3 %)	37 (30.8 %)	0.347
Previous anticoagulant use	1 (2.3 %)	10 (8.3 %)	0.291
Previous antiplatelet use	8 (18.6 %)	15 (12.5 %)	0.324
Hospital admission time (h)	9 (6–18)	8 (5–13)	0.202
Blood sampling time (h)	10 (7–19)	9 (6–14)	0.253
Dysphasia	14 (32.6 %)	18 (15.0 %)	0.013
Vomiting	14 (32.6 %)	21 (17.5 %)	0.039
Systolic arterial pressure (mmHg)	146.3 ± 28.4	145.8 ± 21.5	0.904
Diastolic arterial pressure (mmHg)	85.5 ± 9.8	85.1 ± 9.7	0.784
Hemorrhagic locations (superficial/deep)	13/30	37/83	0.942
Intraventricular extension of hematoma	12 (27.9 %)	21 (17.5 %)	0.145
Subarachnoidal extension of hematoma	5 (11.7 %)	11 (9.2 %)	0.642
NIHSS scores	13 (12–16)	9 (7–12)	<0.001
Hematoma volume (ml)	17 (13–23)	9 (7–12)	<0.001
Blood leucocyte count (× 10^9/l)	8.0 (4.8–9.8)	6.9 (5.2–9.1)	0.686
Blood glucose levels (mmol/l)	11.5 (7.9–16.6)	9.2 (7.5–11.2)	0.018
Serum AIM2 levels (ng/ml)	6.3 (3.4–12.0)	2.7 (1.3–6.5)	<0.001

Data were presented as count (percentage), mean ± 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. NIHSS indicates National Institutes of Health Stroke Scale; SAP, stroke-associated pneumonia; COPD, chronic obstructive pulmonary disease; AIM2, absent in melanoma 2.

It is well-known that stroke severity, which is often indicated by NIHSS scores and the volume of hematoma, is a conventional determinant of SAP and poor prognosis [4–7,33]. In the present study, serum AIM2 levels took possession of significantly efficient predictive capability for SAP and unfavorable prognostic outcomes after ICH, and moreover, in comparison to NIHSS scores and the volume of hematoma, their predictive abilities were similar with regard to AUC. Furthermore, NIHSS scores, the volume of hematoma and serum AIM2 were integrated into a combination model for predicting SAP and poor prognosis. By employing various statistical

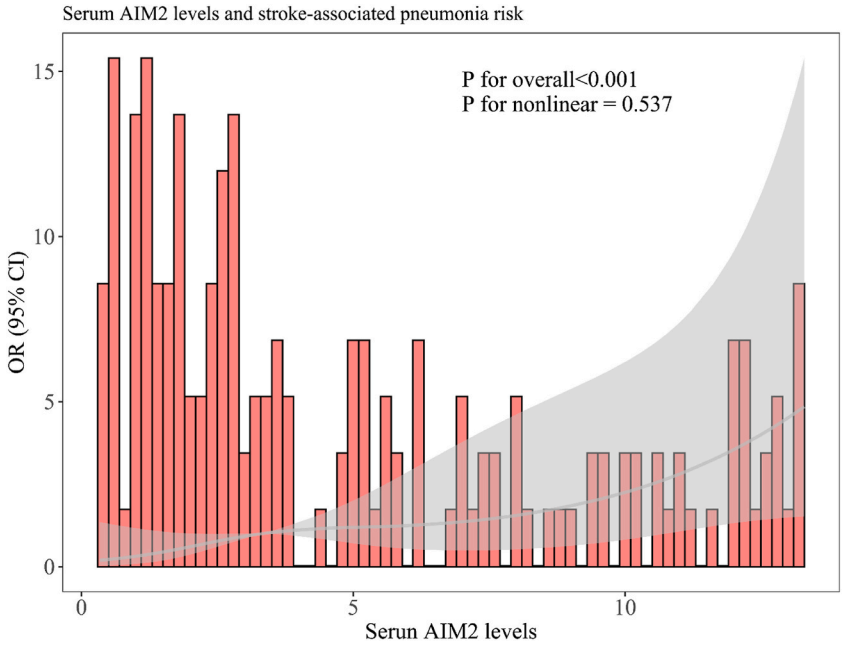

Fig. 11. Restricted cubic spline indicating the direct relationship between serum absent in melanoma 2 concentrations and the likelihood of stroke-associated pneumonia following acute intracerebral hemorrhage. Serum levels of absent in melanoma 2 displayed a linear correlation with the likelihood of stroke-associated pneumonia following intracerebral hemorrhage. AIM2 denotes absent in melanoma 2; OR, odds ratio; 95 % CI, 95 % confidence interval.

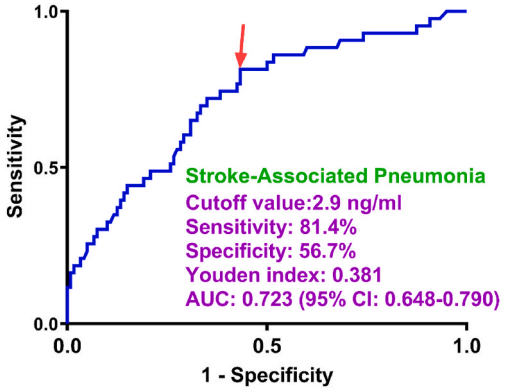

Fig. 12. Receiver operating characteristic plot assessing stroke-associated pneumonia predictive ability of serum absent in melanoma 2 levels after acute intracerebral hemorrhage. Serum absent in melanoma 2 concentrations efficiently discriminated risk of stroke-associated pneumonia after hemorrhagic stroke. Employing the Youden approach, the threshold value of serum absent in melanoma 2 levels was chosen, which predicted stroke-associated pneumonia along with its associated sensitivity and specificity. AUC means area under curve; 95 % CI, 95 % confidence interval.

techniques, such as ROC curve analysis, calibration curve analysis and decision curve analysis, the model demonstrated effectiveness in forecasting adverse six-month outcomes, but not for predicting SAP. Thus, serum AIM2 integrated with NIHSS scores and the volume of hematoma may be a good choice for prognosis prediction of ICH.

This study possesses both strengths and limitations. The advantages include that (1) to our current understanding, this may be an initial set for determining blood AIM2 levels after ICH; (2) fluctuations in serum AIM2 concentrations over time were investigated from admission until day 14 after ICH; (3) multiple multivariate models were built for severity assessment and prognosis correlation study. The weaknesses are that (1) although serum AIM2 were verified in this study as a promising prognostic indicator of ICH in a medium sample size, such a conclusion needs validation in a larger cohort investigation; (2) because a small number of patients consented for blood samples collected at various intervals, it is impossible to discern when serum AIM2 levels could the most efficiently predict clinical outcomes of ICH. In order to overcome such a difficulty, it is a good choice to increase the sample size.

Table 5
Subgroup analysis and intersubgroup interaction analysis between serum absent in melanoma levels and stroke-associated pneumonia after acute intracerebral hemorrhage.

Subgroup analysis		Total (n)	OR (95 % CI)	P value	$P_{interaction}$ value
Age	≥65 years	78	1.250 (1.060–1.473)	0.008	0.137
	<65 years	85	0.932 (0.791–1.099)	0.403	
Gender	Male	93	1.275 (1.100–1.265)	0.001	0.075
	Female	70	1.076 (0.942–1.228)	0.281	
Cigarette consumption	Yes	63	1.045 (0.907–1.204)	0.544	0.268
	No	100	1.209 (1.054–1.387)	0.007	
Alcohol consumption	Yes	70	1.151 (0.992–1.337)	0.064	0.195
	No	93	1.216 (1.076–1.373)	0.002	
Hypertension	Yes	105	1.183 (1.028–1.363)	0.019	0.065
	No	58	1.068 (0.927–1.229)	0.364	
Diabetes mellitus	Yes	36	1.075 (0.956–1.208)	0.227	0.257
	No	127	1.254 (1.036–1.518)	0.020	
Dyslipidemia	Yes	57	1.032 (0.905–1.177)	0.635	0.215
	No	106	1.331 (1.061–1.670)	0.014	
Previous statin use	Yes	47	1.152 (0.895–1.483)	0.272	0.141
	No	116	1.206 (1.059–1.373)	0.015	
Previous antiplatelet use	Yes	23	1.034 (0.766–1.396)	0.828	0.092
	No	140	1.127 (1.011–1.256)	0.031	

Associations were adjusted for dysphasia, vomiting, National Institutes of Health Stroke Scale scores, hematoma volume and blood glucose levels. OR denotes odds ratio; 95 % CI, 95 % confidence interval.

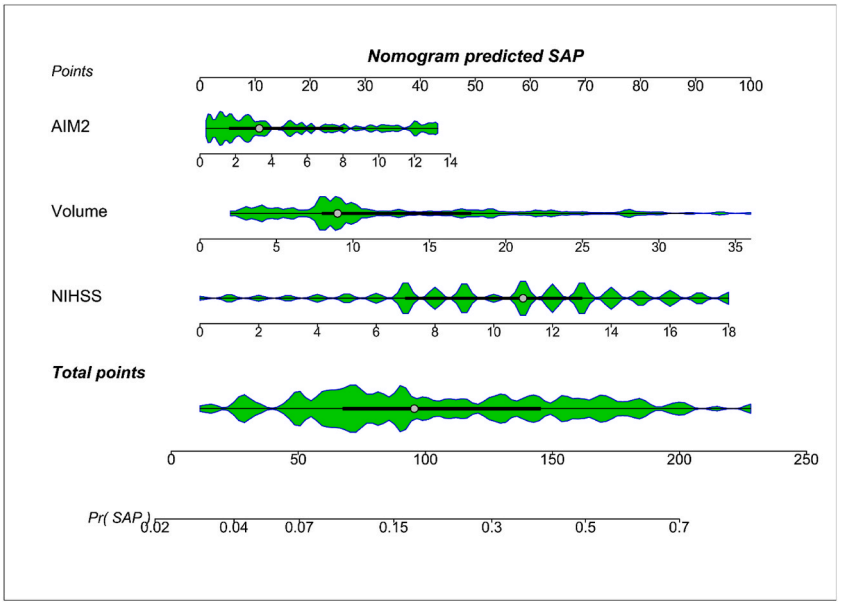

Fig. 13. Nomogram evaluating the stroke-associated pneumonia prediction model of individuals experiencing acute intracerebral hemorrhage. Serum absent in melanoma 2, hematoma volume and National Institutes of Health Stroke Scale scores were merged to discriminate risk of stroke-associated pneumonia subsequent to acute intracerebral hemorrhage. NIHSS denotes National Institutes of Health Stroke Scale; AIM2, absent in melanoma 2.

5. Conclusions

In contrast to healthy individuals, there is a notable increase in serum AIM2 concentrations from admission to day 14 after ICH. Serum AIM2 concentrations display autonomous associations with NIHSS scores and the volume of hematoma, in addition to are linearly related to and independently associated with risks of SAP and an unfavorable outcome at the 6-month mark following ICH. The model incorporating serum AIM2, NIHSS scores, and the volume of hematoma performs well for predicting poor prognosis. In summary, serum AIM2, as a promising prognostic indicator, could offer valuable insights in the medical management of ICH.

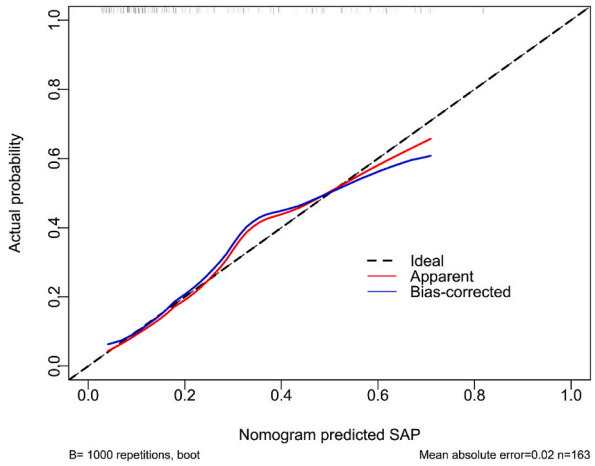

Fig. 14. Graph assessing the reliability of a nomogram in distinguishing the likelihood of stroke-associated pneumonia following acute intracerebral hemorrhage. The confirmed framework maintained a consistent level of reliability in forecasting pneumonia linked with stroke subsequent to sudden intracerebral bleeding.

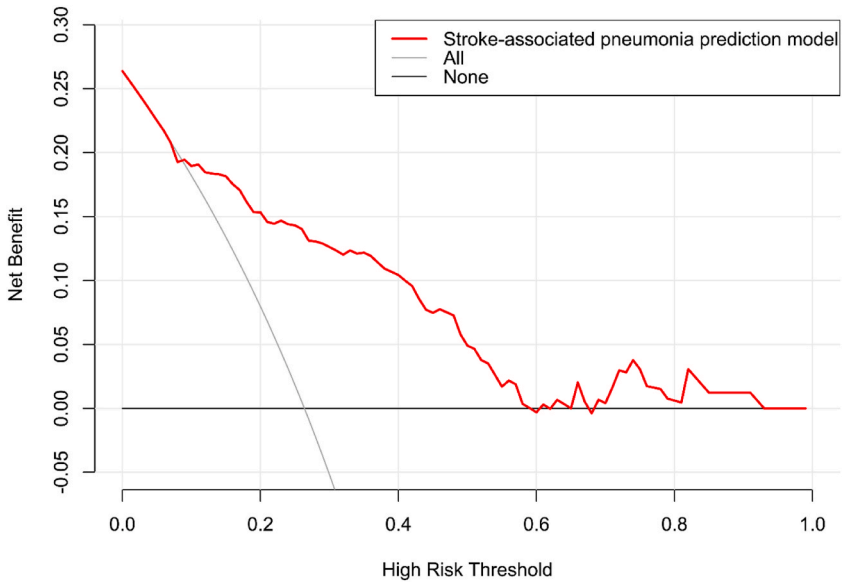

Fig. 15. Assessment graph confirming the practical applicability of the model in identifying the likelihood of stroke-associated pneumonia. The built model was clinically fit for predicting stroke-associated pneumonia after intracerebral hemorrhage.

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Data availability statement

The study data has not been stored in a publicly accessible repository. However, interested parties may request access to the data from the corresponding author upon inquiry.

CRediT authorship contribution statement

Chengliang Zhang: Writing – review & editing, Writing – original draft, Validation, Software, Investigation, Funding acquisition, Data curation, Conceptualization. **Chuanliu Wang:** Writing – original draft, Supervision, Software, Resources, Methodology, Data

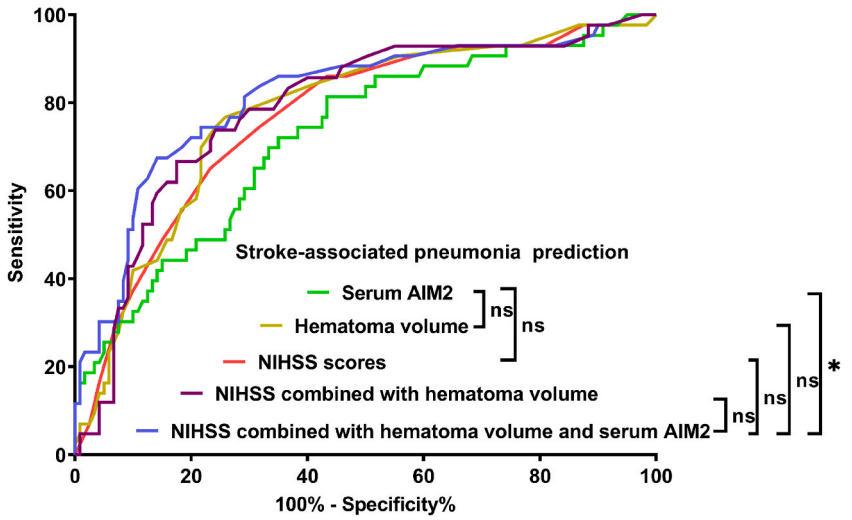

Fig. 16. Plotting the receiver operating characteristic curve to evaluate the predictive capacity of serum absent in melanoma 2 concentrations and a combined model for stroke-associated pneumonia following sudden intracerebral bleeding. Serum absent in melanoma 2 concentrations had similar stroke-associated pneumonia predictive ability, as compared to National Institutes of Health Stroke Scale scores and the volume of hematoma. Combination of National Institutes of Health Stroke Scale scores with the volume of hematoma and serum absent in melanoma 2 showed significantly higher stroke-associated pneumonia predictive ability, as opposed to serum absent in melanoma 2 levels. AIM2 means absent in melanoma 2; NIHSS, National Institutes of Health Stroke Scale; ns, non-significant. *P < 0.05.

curation. **Ming Yang:** Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Han Wen:** Visualization, Validation, Supervision, Software, Resources, Data curation, Conceptualization. **Ping Li:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paperThe authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ping Li reports financial support was provided by Clinical Research Fund Project of Zhejiang Medical Association (2021ZYC-A210). If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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