Dynamic serum amyloid A for the prediction of the trajectory of ventilator-associated pneumonia in elderly patients with acute ischemic stroke undergoing endovascular therapy and general anesthesia

Keywords
endovascular therapy, acute ischemic stroke (AIS), ventilator-associated pneumonia (VAP), dynamic serum amyloid A (SAA)

Abstract

Introduction

In patients with acute ischemic stroke (AIS), current models for predicting ventilator-associated pneumonia (VAP) predominantly rely on multi-parameter approaches, which significantly increase data collection complexity and hinder clinical implementation. Here, we further investigate VAP-related risk factors while dynamically analyzing the predictive value of serum amyloid A (SAA) levels for VAP, aiming to bridge the gap between biomarker-driven simplicity and clinical practicality.

Material and methods

387 patients were ultimately enrolled and divided into two groups: non-VAP (n = 278) and VAP (n = 109). The least absolute shrinkage and selection operator (LASSO), univariate and multivariate logistic regression analyses were utilized to examine the independent risk factors associated with VAP. Calibration and decision curve analysis (DCA) curves were employed to assess the model's goodness of fit.

Results

A VAP prediction model incorporating seven multimodal clinical parameters, age, mechanical ventilation duration, DBP, admission NIHSS score, hs-CRP, TC, and SAA-T2, was developed, achieving exceptional predictive performance with an AUC (95% CI) of 0.961 (0.942-0.980). Based on single-parameter AUC values and DCA, SAA-T2 demonstrated the highest diagnostic efficacy and net clinical benefit. The diagnostic performance of Model1 and SAA-T2 yielded AUCs (95% CI) of 0.889 (0.853-0.924) and 0.885 (0.842-0.928), respectively, with no statistically significant difference between them. Notably, the addition of SAA-T2 to Model1 significantly enhanced its diagnostic accuracy for VAP.

Conclusions

We developed an excellent nomogram model incorporating seven clinical parameters to predict VAP. SAA-T2 may serve as a rapid and practical clinical indicator for predicting VAP in AIS patients, balancing accuracy with clinical feasibility.

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Running title: Dynamic SAA for predicting VAP.

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Keywords: dynamic serum amyloid A (SAA); acute ischemic stroke (AIS); ventilator-associated pneumonia (VAP); endovascular therapy

Introduction

Acute ischemic stroke (AIS), characterized by impaired cerebral perfusion with high morbidity, disability, and mortality rates, commonly requires endovascular treatment (EVT) [1]. In this context, general anesthesia has become a cornerstone technique for EVT protocols, offering critical advantages including airway protection, complete motion control, and enhanced intraoperative imaging quality to optimize procedural outcomes [2]. However, prolonged mechanical ventilation carries an elevated risk of ventilator-associated pneumonia (VAP), with studies indicating that postoperative VAP incidence rates may approach 50% in this patient population [2]. VAP is a type of hospital-acquired pneumonia and a common complication in patients with mechanical ventilation [3, 4]. VAP is defined as pneumonia occurring 48 hours after endotracheal intubation or tracheostomy for mechanical ventilation and up to 48 hours after extubation [3]. Studies worldwide report that the incidence and mortality rates of VAP can reach as high as 50% and 70%, respectively [5-7]. The development of VAP is associated with airway damage, impaired cough reflex, compromised mucociliary clearance, and bacterial colonization (including pathogens such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*) [5, 8-10]. Bacterial antibiotic resistance has become a major global public health challenge, particularly in the treatment of VAP. Therefore, early recognition of VAP is critical for timely diagnosis and improved clinical outcomes. Currently, there is no definitive gold standard for diagnosing VAP [5, 11]. Diagnosis primarily relies on new or progressive infiltrates on chest X-ray or CT, combined with at least two of the

following clinical criteria: fever, neutrophilia (>10×10^9/L) or neutropenia (<5×10^9/L), and purulent sputum [5]. The complexity of diagnosis significantly hampers the rapid clinical identification of VAP.

Serum Amyloid A (SAA) is an acute-phase reactant synthesized by the liver and belongs to the apolipoprotein family [12]. SAA levels rise significantly in response to inflammation, infection, or tissue injury, making it a critical biomarker for assessing inflammatory status. Compared to C-reactive protein (CRP), SAA exhibits earlier and more sensitive elevation during inflammatory processes [13]. Elevated SAA levels are strongly associated with cardiovascular diseases and serve as an independent predictor of cardiovascular events [14-16]. In addition, elevated SAA levels have been associated with post-stroke inflammation, post-stroke cognitive impairment and poor prognosis in AIS patients undergoing intravenous thrombolysis [12, 17-21]. SAA may be an available predictor for VAP with a sensitivity and specificity of 100% 93.1%, respectively [22]. SAA also serves as valuable prognostic indicators for postoperative VAP in elderly patients undergoing abdominal surgery with tracheal intubation and general anesthesia [23]. More intriguingly, the measurement levels of SAA at different time points predict distinct prognostic capabilities [12], highlighting the critical clinical significance of dynamic SAA monitoring.

Although SAA has shown potential as a biomarker for predicting VAP, the differential predictive value of dynamic SAA levels in VAP remains unreported. This study aims to enroll elderly patients with AIS undergoing endovascular therapy and general anesthesia, with or without VAP. By dynamically measuring serum SAA levels at

three distinct time points, pre-operation, 48 hours post-mechanical ventilation, and 96 hours post-mechanical ventilation, we will evaluate the variations in SAA's predictive efficacy for VAP in this cohort population.

Methods

Study participants and design. We conducted a retrospective analysis of clinical data from 641 AIS patients treated with endovascular therapy under general anesthesia between January 2020 and December 2024. Inclusion criteria required confirmation of AIS diagnosis according to the American Heart Association/American Stroke Association (AHA/ASA) guidelines [24]. The study excluded participants based on the following criteria: (1) secondary transport for stroke (n = 27); (2) preoperative pneumonia (n = 35); (3) trauma (n = 22); (4) with a recent history of cardiopulmonary resuscitation or established artificial airway (n = 7); (5) died during postoperative within 96 h (n = 6); (6) with immune, blood, tumor, severe cardiovascular, hepatic, renadisorders, or unstable vital signs (n = 23); (7) data missing and imcomplete medical records (n = 134). Exclusion criteria led to the removal of 254 AIS patients, resulting in a final cohort of 387 individuals who underwent endovascular therapy under general anesthesia. Among 641 AIS patients who underwent endovascular therapy and general anesthesia, a total of 254 patients were excluded, and 387 patients were ultimately enrolled in the study. These 387 AIS patients were divided into two groups: non-VAP (n = 278) and VAP (n = 109) (**Figure 1**). The authors assume full responsibility for study design, data interpretation, and resolution of any concerns related to data accuracy or methodological rigor. The protocol adhered to the ethical principles of the Declaration of Helsinki (2013 revision) and followed the TRIPOD guidelines (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) [25], with institutional ethics committee approval obtained prior to data collection (Approval number: 202409025).

Primary and secondary clinical outcomes. The diagnostic criteria for VAP were defined according to prior studies, and perioperative anesthetic management protocols

were guided by established clinical guidelines [23]. The diagnosis of VAP requires meeting specific criteria: radiographic evidence of new or progressive abnormalities on chest X-ray/CT scan combined with at least two clinical manifestations from the following: (1) fever (body temperature >38°C); (2) purulent respiratory secretions; (3) leukocyte count >10 × 10^9/L or <4 × 10^9/L; (4) presence of cough, dyspnea, or tachypnea (respiratory rate >25 breaths per minute). The primary outcome of this study was the development of a VAP prediction model, while the secondary outcomes focused on examining the association between SAA levels measured at serial time points and VAP occurrence, as well as evaluating the predictive performance of other clinical indicators. 30-day mortality was the mainly prognostic parameter in our study.

Data collection and laboratory test. General information, including age, gender, Time of mechanical ventilation, body mass index (BMI), hypertension history, systolic blood pressure (SBP), diastolic blood pressure (DBP), Diabetes history, Stroke history, Time of operation, Trial of ORG 10172 in acute stroke treatment (TOAST), hyperlipidemia, fasting blood glucose (FBG), hemoglobin, thrombolysis in cerebral infarction (TICI), length of stay (LOS), national Institute of Health stroke scale (NIHSS) Glasgow Coma Scale (GCS), modified Rankin Scale (mRs), creatinine (Cre) with enzymatic assay, homocysteine (Hcy) with fluorescence polarization immunoassay (FPIA), uric acid (UA) with enzymatic colorimetric, D-Dimer (D-D) with chemiluminescent immunoassay (CLIA), high-sensitivity C reactive protein (hs-CRP) with immunonephelometry, triglycerides (TG) with enzymatic method, total cholesterol (TC) with enzymatic method, low-density lipoprotein cholesterol (LDL-C) with homogeneous direct assay (polyethylene glycol-modified enzymes), high-density

lipoprotein cholesterol (HDL-C) with homogeneous precipitation (accelerated surfactant method), serum amyloid A (SAA) at pre-operation (T1), 48 hours post-mechanical ventilation (T2), and 96 hours (T3) post-mechanical ventilation, were collected to filtrate VAP-related risk factors. The concentration of serum SAA was measured by a commercially available kit with scattering nephelometry (Cat. no: OQMP11; Siemens Healthcare Diagnostics Products GmbH, Munich, Germany; intra-assay CV ≤6.2%, inter-assay CV ≤4.7%, and total CV ≤6.4%) with an automatic biochemical analyser (ADVIA 2400, Siemens, Munich, Germany). The diagnostic criteria for hyperlipidemia were established in accordance with the NCEP-ATP III guidelines, with biochemical cutoff values defined as follows: TC ≥6.2 mmol/L; LDL-C ≥4.1 mmol/L; and TG ≥2.3 mmol/L. The biochemical marker analysis was conducted using the Mindray BS-800M fully automatic biochemical analyzer. Intra-assay coefficient of variation: < 5% (enzymatic indicators), < 8% (immunoassay indicators); Inter-assay coefficient of variation: < 7% (enzymatic indicators), < 10% (immunoassay indicators).

Statistical methods. Statistical analyses were performed using IBM SPSS Statistics (version 25.0, IBM, Armonk, NY, USA), GraphPad Prism 9.0 (GraphPad Software, Inc., La Jolla, CA, USA), and R software (version 4.2.1) with the survival package (version 3.3.1), rms package (version 6.3-0), timeROC package (version 0.4), and ggplot2 package (version 3.3.6). Descriptive statistics, such as the median and interquartile range (IQR) for non-normally distributed data or the mean and standard deviation for normally distributed data, were calculated. The study utilized Fisher's

exact test or chi-square test for categorical variables, Wilcoxon signed-rank test for continuous variables, t-tests, and Mann-Whitney test for group differences assessment. Comparisons among the three groups were performed using the omnibus Kruskal-Wallis test, followed by Dunn's test for post-hoc multiple comparisons. Sankey diagrams were visualized using the ggplot2 package (version 3.4.4) and ggalluvial package (version 0.12.3). The independent risk factors associated with VAP were examined through the least absolute shrinkage and selection operator (LASSO) and the binary logistic regression analysis. Receiver operating characteristic (ROC) curves with area under the curve (AUC) was used to evaluate the predictive effectiveness of risk factors. LASSO regression was employed to assess the prognostic correlation coefficient, while the glmnet package (version 4.1.7) was utilized for the analysis of the processed data in order to determine the variable lambda value, maximum likelihood number or C-index with R software (version 4.2.1). The glm function was utilized to develop a binary logistic model, while the rms (version 6.4.0) and ResourceSelection (version 0.3-5) packages were employed to construct a nomogram model and facilitate its visualization. The goodness-of-fit of the nomogram model was assessed using statistical measures such as the likelihood-ratio test, C index, and hosmer-lemeshow goodness fit. The rms package (version 6.3-0) was utilized for calibration analysis and data visualization. The stdca.R file was employed for conducting decision curve analysis (DCA). A two-tailed approach was employed for all statistical analyses, with statistical significance defined as p-values less than 0.05.

Results

Population characteristics and baseline data. We collected 31 clinical parameters, and 12 parameters showed significant intergroup differences, including age, time of mechanical ventilation, hypertension history, DBP, TICI score, admission NIHSS, hs-CRP, LDL-C, SAA-T1, SAA-T2, SAA-T3, and 30-day mortality (**Table 1**). Compared with non-VAP patients, VAP patients had a higher age, proportion of those with mechanical ventilation duration > 2 days, diastolic blood pressure, proportion of those with TICI score (0-2a), admission NIHSS score, hs-CRP level, LDL-C level, and significantly increased SAA-T1 at three different time points. Moreover, the mortality rate also significantly increased in VAP patients compared with those of non-VAP patients (**Table 1**).

SAA level associated with VAP in AIS patients. Compared to non-VAP patients, serum SAA levels at three different timepoints (T1, T2, T3) were significantly elevated in VAP patients (**Figure 2A**). Additionally, SAA levels at T2 and T3 were significantly higher than those at T1 in VAP patients. However, no significant difference was observed between T2 and T3 timepoints in VAP patients (**Figure 2B**). Furthermore, using a Sankey diagram to dynamically visualize the correlation between SAA level changes and VAP, we found that higher SAA levels were more likely to be associated with postoperative VAP occurrence (**Figure 2C**).

Screening of VAP-related risk factors in AIS patients. First, we performed LASSO regression analysis, including LASSO coefficient screening (**Figure 3A**) and variable trajectory plots (**Figure 3B**), which identified 8 non-zero coefficients associated with

VAP in AIS patients. Subsequently, univariate and multivariate logistic regression analyses were used to identify VAP-related risk factors in AIS patients. The results revealed that the following 7 clinical parameters were independent risk factors for VAP development: age (OR = 1.096; 95% CI: 1.032–1.164; P = 0.003), time of mechanical ventilation > 2 days (OR = 3.990; 95% CI: 1.721–9.247; P = 0.001), DBP (OR = 1.174; 95% CI: 1.030–1.339; P = 0.017), admission NIHSS score (OR = 1.309; 95% CI: 1.145–1.497; P < 0.001), hs-CRP (OR = 1.143; 95% CI: 1.045–1.250; P = 0.004), TC (OR = 2.297; 95% CI: 1.221–4.320; P = 0.010), and SAA-T2 (OR = 1.104; 95% CI: 1.076–1.132; P < 0.001) (**Table 2**).

Establishment of a nomogram for predicting VAP of patients with AIS. We constructed a nomogram for predicting VAP in AIS patients using seven clinical parameters: age, time of mechanical ventilation, DBP, admission NIHSS score, hs-CRP, TC, and SAA-T2. The prediction method involves calculating individual scores for each parameter, summing them to obtain a total score, and then drawing a vertical line from the total score axis to determine the corresponding VAP risk probability (**Figure 4A**). Likelihood ratio test (P < 0.05) indicated that at least one variable in the model had a statistically significant OR, and the overall model was meaningful. Discrimination ability was evaluated using the C-index (95% CI), which was 0.961 (95% CI: 0.941–0.981), demonstrating excellent predictive accuracy. Calibration performance was assessed by the Hosmer-Lemeshow goodness-of-fit test (P = 0.945), indicating no significant difference between predicted and observed outcomes, thus confirming good model fit (**Figure 4B**). DCA was used to evaluate the

net benefit of clinical interventions based on model predictions across varying high-risk probability thresholds. Each curve represents the net benefit of interventions guided by a specific variable as the threshold changes. Here, “All” indicates intervening on the entire population, while “None” indicates no intervention (net benefit remains 0). The intersection point of the All and None curves represents the threshold at which intervening on all patients (regardless of risk) and intervening on none yield equivalent net benefits. As the high-risk probability threshold increases, the net benefit of model-guided interventions declines. Among the seven clinical parameters, SAA-T2 exhibited the highest net benefit, indicating its highest clinical utility for guiding VAP risk stratification in AIS patients (**Figure 4C**).

ROC analysis was performed to evaluate the predictive efficiency of risk factors for VAP in AIS patients. We subsequently performed ROC-AUC analysis to evaluate the predictive performance of individual risk factors for VAP. The AUC (95% CI) values of age, time of mechanical ventilation, DBP, admission NIHSS score, hs-CRP, TC, and SAA-T2 were 0.639 (0.576-0.701), 0.629 (0.576-0.683), 0.724 (0.672-0.776), 0.755 (0.698-0.812), 0.617 (0.552-0.683), 0.543 (0.477-0.610), 0.885 (0.842-0.928), respectively (**Table 3 and Figure 5**).

ROC analysis was performed to evaluate the predictive efficiency of combined models for VAP in AIS patients. We further developed two combined models. Model1 included six parameters: age, time of mechanical ventilation, DBP, admission NIHSS score, hs-CRP, and TC. Model2 was constructed by adding SAA-T2 to Model 1. The diagnostic performance of Model2 [AUC (95% CI) = 0.961 (0.942-0.980)] was

significantly superior to that of Model1 [AUC (95% CI) = 0.889 (0.853-0.924)], indicating that incorporating SAA-T2 substantially improved the predictive power of Model 1 for VAP in patients with AIS. No significant difference was observed between the diagnostic performance of Model 1 and SAA-T2 alone (P = 0.905) (**Table 4 and Figure 6**). These results strongly support that SAA-T2 (cut-off value = 51.11 mg/L) is a robust and efficient clinical indicator for rapid diagnosis of VAP in AIS patients.

SAA level associated with poor prognosis of AIS patients. We evaluated 30-day mortality as a prognostic parameter for AIS patients undergoing endovascular therapy. The results revealed that non-survivors (patients who died within 30 days) exhibited significantly elevated serum SAA levels at three distinct time points compared to 30-day survivors: T1 (52.25 ± 20.78 mg/L vs. 41.43 ± 14.93 mg/L; P < 0.001), T2 (72.54 ± 25.99 mg/L vs. 44.77 ± 16.97 mg/L; P < 0.001), and T3 (; 71.74 ± 26.48 mg/L vs. 46.3 ± 17.42 mg/L; P < 0.001) (**Figure 7**).

Discussion

In summary, we evaluated SAA levels at three distinct timepoints and observed that SAA levels were significantly elevated at all three time points in VAP patients. Higher SAA levels were associated with an elevated risk of VAP. Subsequent LASSO regression combined with logistic regression analysis identified SAA-T2 as the optimal clinical indicator for predicting VAP. Additionally, we developed a nomogram model incorporating seven clinical parameters to predict VAP, which demonstrated excellent discrimination [C-index (95% CI) = 0.961 (0.941–0.981)]. Although the combined model showed superior predictive performance, AUC (0.961; 95%: 0.942-0.980) and DCA analyses revealed that SAA-T2 alone exhibited high diagnostic power and net benefit rate. We conclude that SAA-T2 may serve as a rapid and practical clinical indicator for predicting VAP in AIS patients, balancing accuracy with clinical feasibility.

VAP is a severe complication in patients with traumatic brain injury and AIS. Studies have reported that smoking, tracheostomy, blood transfusion on admission, injury severity score (ISS), Glasgow Coma Scale (GCS) score, ICU length of stay, dysphagia, duration of mechanical ventilation, hemorrhagic conversion, Fazekas scale grade 2, admission DBP are associated with VAP development [2, 7, 26, 27]. Frondelius et al. [7] developed a VAP prediction model incorporating duration of mechanical ventilation, length of ICU stay, blood transfusion, nutrition strategy, and presence of antibiotics, which demonstrated robust performance with an AUC of 0.88 (95% CI: 0.82-0.94), sensitivity of 0.72 (95% CI: 0.45-0.98), and specificity of 0.90

(95% CI: 0.85-0.94). Zhu et al. [2] developed a VAP nomogram model for patients with large vessel occlusion stroke, incorporating GCS score, ICU length of stay, dysphagia, Fazekas scale grade 2, and admission diastolic blood pressure, which demonstrated strong predictive accuracy with an AUC of 0.862 (95% CI: 0.810-0.914). Li et al. [28] identified ICU length of stay, surgery, CRP levels, and number of reintubations as independent risk factors for VAP in elderly ICU patients requiring mechanical ventilation. The predictive model demonstrated robust performance, with AUC values of 0.859 (95% CI: 0.828-0.890) in the training set and 0.813 (95% CI: 0.700-0.850) in the validation set for predicting VAP [28]. In our study, a VAP prediction model incorporating seven multimodal clinical parameters, age, mechanical ventilation duration, DBP, admission NIHSS score, hs-CRP, TC, and SAA-T2, was developed, achieving exceptional predictive performance with an AUC (95% CI) of 0.961 (0.942-0.980). Based on single-parameter AUC values and DCA, SAA-T2 demonstrated the highest diagnostic efficacy and net clinical benefit. Further, the seven parameters were split into two models: Model1 (age, mechanical ventilation duration, DBP, NIHSS score, hs-CRP, TC) and SAA-T2 alone. The diagnostic performance of Model1 and SAA-T2 yielded AUCs (95% CI) of 0.889 (0.853–0.924) and 0.885 (0.842–0.928), respectively, with no statistically significant difference between them. Notably, the addition of SAA-T2 to Model 1 significantly enhanced its diagnostic accuracy for VAP. These findings suggest that SAA-T2 serves as a rapid and concise biomarker for predicting postoperative VAP in AIS patients, while its

combination with other clinical parameters (age, mechanical ventilation duration, DBP, NIHSS score, hs-CRP, TC) achieves superior performance.

A few studies have suggested a potential association between SAA and VAP [22, 23, 29]. Specifically, baseline SAA levels at enrollment were significantly higher in the early VAP group compared to the non-early VAP group. At a cut-off value of 224 mg/mL, baseline SAA demonstrated 84% sensitivity and 72.7% specificity for predicting early VAP, with an AUC of 0.76, highlighting its discriminative capacity in this clinical setting [29]. Lin et al. [23] discovered that in patients undergoing abdominal surgery, SAA levels at 24 h postoperatively demonstrated moderate predictive utility for VAP, with an AUC of 0.68, sensitivity of 73.24%, and specificity of 55.16%. Abo-Hagar et al. [22] reported that SAA demonstrated exceptional diagnostic performance for predicting VAP in mechanically ventilated pediatric patients, achieving an AUC of 0.97 (95% CI: 0.86–1.00), sensitivity of 100%, and specificity of 93.1%. These results underscore the potential of SAA as a highly reliable biomarker for early VAP detection in critically ill children requiring mechanical ventilation [22]. In our study, we focused on the association between SAA and VAP in elderly AIS patients undergoing general anesthesia and endovascular therapy. Although there were differences in SAA among the three time points, after LASSO and logistic regression analysis, SAA-T2 was found to be an independent risk factor for VAP. Therefore, SAA-T2 was selected as a predictor of VAP. Since SAA-T2 is a postoperative indicator, it indicates that the acute-phase inflammatory response after surgery can better reflect the risk of VAP. We observed a significant increase in

SAA levels at 48 hours postoperatively compared to preoperative baseline. Notably, postoperative 48-hour SAA levels emerged as the strongest independent predictor of VAP, demonstrating an AUC of 0.885 (95% CI: 0.842–0.928), sensitivity of 81.7%, and specificity of 92.4%. While our findings, alongside existing evidence [22, 23, 29], highlight the clinical utility of SAA in VAP prediction, its diagnostic performance may vary across populations and disease contexts.

Plasma SAA levels at 24 hours after EVT serve as a significant predictor of poor functional outcome at 3 months in stroke patients [12]. Moreover, SAA levels at 24 hours post-EVT were significantly higher compared to pre-EVT SAA levels, and SAA levels at different time points exhibit distinct prognostic values in stroke patients [12]. Chang et al. [18] also found that SAA levels were up-regulated during hospitalization in AIS patients after intravenous thrombolysis. No previous studies have reported on the dynamic changes in SAA levels among AIS patients complicated by VAP. This gap underscores the novelty of our investigation, which systematically evaluates temporal SAA trajectories in this high-risk population to uncover its potential role in early VAP detection and prognosis. We found that SAA levels at three distinct timepoints were significantly associated with 30-day mortality in AIS patients. Compared to survivors, patients who died within 30 days exhibited markedly elevated SAA levels. Our findings, consistent with prior evidence [12, 18], confirm that SAA may serve as a robust prognostic biomarker for adverse outcomes in AIS, reflecting its potential role in stratifying mortality risk and guiding early intervention strategies.

Our study has several limitations. First, the relatively small sample size may introduce potential bias in the results. Second, we only collected SAA data at three timepoints in AIS patients, lacking comprehensive measurements throughout the hospitalization period. Third, we focused solely on 30-day prognosis and did not implement a long-term follow-up plan. In future studies, we will conduct extended follow-up to further explore the relationship between SAA and long-term outcomes in VAP patients.

Conclusion

In summary, we developed a highly sensitive predictive model based on seven clinical parameters to forecast postoperative VAP in AIS patients. Among these parameters, SAA demonstrated the highest diagnostic efficacy and played a pivotal role in ensuring model stability. We propose that postoperative 48-hour SAA levels could serve as a rapid and sensitive indicator for estimating the likelihood of VAP in AIS patients, particularly when additional clinical parameters are unavailable.

Declaration

Funding: Not applicable.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors have no conflicts of interest to declare.

Authors' contributions: Study design was performed by P-S, Y-J; Literature research was performed by P-S and Y-J; Data acquisition and Statistical analysis were executed by P-S; Manuscript writing and editing were performed by P-S and Y-J; Manuscript review was performed by P-S and Y-J; Manuscript was approved by all authors.

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Figure legends

Figure 1. Flowchart of participant enrollment, model development, and validation. AIS, acute ischemic stroke; VAP, ventilator-associated pneumonia; LASSO, least absolute shrinkage and selection operator; ROC, receiver operating characteristic.

Figure 2. SAA level associated with VAP in AIS patients. Serum SAA levels at three different timepoints (T1, T2, T3) were analyzed in AIS patients with or without VAP (A). SAA levels at T1, T2 and T3 were compared in VAP patients (B). Using a Sankey diagram to dynamically visualize the correlation between SAA level changes and VAP in patients with AIS (G1≤ 30 mg/L; 30 mg/L<G2 ≤ 50 mg/L; G3 > 50 mg/L) (C). T1, pre-operation; T2, 48 hours post-mechanical ventilation; T3, 96 hours post-mechanical ventilation. SAA, serum amyloid A; AIS, acute ischemic stroke; VAP, ventilator-associated pneumonia. ns, no significance; $^{**}P < 0.01$; $^{***}P < 0.001$.

Figure 3. Screening of VAP-related risk factors in AIS patients with LASSO. LASSO regression analysis, including LASSO coefficient screening (A) and variable trajectory plots (B), was used to identify non-zero coefficients associated with VAP in AIS patients. LASSO, least absolute shrinkage and selection operator; VAP, ventilator-associated pneumonia; AIS, acute ischemic stroke.

Figure 4. Establishment of a nomogram for predicting VAP of patients with AIS. We constructed a nomogram for predicting VAP in AIS patients using seven clinical parameters: age, time of mechanical ventilation, DBP, admission NIHSS score, hs-CRP, TC, and SAA-T2 (A). Nomogram model was verify with calibration curve with the Hosmer-Lemeshow goodness-of-fit test (B) and DCA (C). VAP,

ventilator-associated pneumonia; AIS, acute ischemic stroke; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C reactive protein; TC, total cholesterol; SAA, serum amyloid A.

Figure 5. ROC analysis was performed to evaluate the predictive efficiency of risk factors for VAP in AIS patients. ROC-AUC was performed to evaluate the predictive performance of individual risk factors for VAP. ROC, receiver operator characteristic curve; AUC, area under the curve; CI; confidence interval; AIS, acute ischemic stroke; VAP, ventilator-associated pneumonia; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C reactive protein; TC, total cholesterol; SAA, serum amyloid A.

Figure 6. ROC analysis was performed to evaluate the predictive efficiency of combined models for VAP in AIS patients. Two combined models were established as follows: Model1 included six parameters: age, time of mechanical ventilation, DBP, admission NIHSS score, hs-CRP, and TC; Model2 was constructed by adding SAA-T2 to Model 1. ROC, receiver operator characteristic curve; AUC, area under the curve; CI; confidence interval; AIS, acute ischemic stroke; VAP, ventilator-associated pneumonia; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C reactive protein; TC, total cholesterol; SAA, serum amyloid A.

Figure 7. SAA level associated with poor prognosis of AIS patients. We evaluated 30-day mortality as a prognostic parameter for AIS patients undergoing endovascular therapy. Differences in SAA levels were evaluated at three distinct timepoints between 30-Day survivors and non-survivors. AIS, acute ischemic stroke; VAP, ventilator-associated pneumonia; SAA, serum amyloid A; T1, pre-operation; T2, 48

hours post-mechanical ventilation; T3, 96 hours post-mechanical ventilation. $^{***}P < 0.001$.

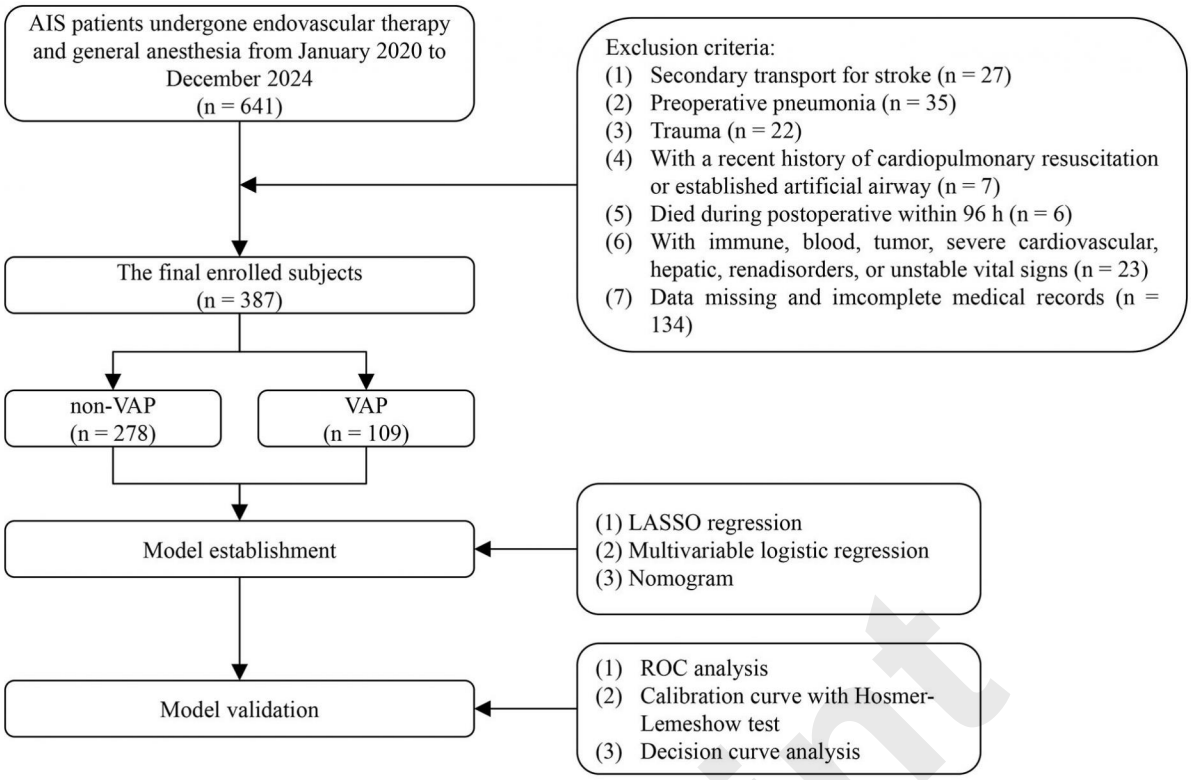
AIS patients undergone endovascular therapy and general anesthesia from January 2020 to December 2024
(n = 641)
Exclusion criteria:
(1) Secondary transport for stroke (n = 27)
(2) Preoperative pneumonia (n = 35)
(3) Trauma (n = 22)
(4) With a recent history of cardiopulmonary resuscitation or established artificial airway (n = 7)
(5) Died during postoperative within 96 h (n = 6)
(6) With immune, blood, tumor, severe cardiovascular, hepatic, renadisorders, or unstable vital signs (n = 23)
(7) Data missing and imcomplete medical records (n = 134)
The final enrolled subjects
(n = 387)
non-VAP
(n = 278)
VAP
(n = 109)
Model establishment
(1) LASSO regression
(2) Multivariable logistic regression
(3) Nomogram
Model validation
(1) ROC analysis
(2) Calibration curve with Hosmer-Lemeshow test
(3) Decision curve analysis

Table 1. Clinical characteristics in elderly patients of AIS with or without VAP.

Characteristics	non-VAP (n = 278)	VAP (n = 109)	P value
Age (years), median (IQR)	71 (67, 77)	75 (70, 81)	< 0.001
Gender, n (%)			0.349
Male	175 (45.2%)	63 (16.3%)	
Female	103 (26.6%)	46 (11.9%)	
Time of mechanical ventilation (days), n (%)			< 0.001
≤ 2	207 (53.5%)	53 (13.7%)	
> 2	71 (18.3%)	56 (14.5%)	
BMI (kg/m^2), median (IQR)	24.1 (21.0, 26.0)	23.9 (20.8, 26.0)	0.862
Hypertension, n (%)			0.003
No	256 (66.1%)	89 (23%)	
Yes	22 (5.7%)	20 (5.2%)	
SBP (mmHg), median (IQR)	129 (125, 133)	129 (125, 133)	0.713
DBP (mmHg), median (IQR)	81 (78, 83)	83 (82, 85)	< 0.001
Hyperlipidemia, n (%)			0.956
No	187 (48.3%)	73 (18.9%)	
Yes	91 (23.5%)	36 (9.3%)	
Diabetes history, n (%)			0.774
No	200 (51.7%)	80 (20.7%)	
Yes	78 (20.2%)	29 (7.5%)	

Stroke history, n (%)			0.170
No	231 (59.7%)	84 (21.7%)	
Yes	47 (12.1%)	25 (6.5%)	
Time of operation, median (IQR)	94 (77, 111)	94 (78, 110)	0.640
TOAST classification, n (%)			0.520
Large-artery atherosclerosis	75 (19.4%)	35 (9%)	
Cardioembolism	62 (16%)	27 (7%)	
Small vessel occlusion	114 (29.5%)	40 (10.3%)	
Others	27 (7%)	7 (1.8%)	
TICI score, n (%)			0.003
2b-3	225 (58.1%)	73 (18.9%)	
0-2a	53 (13.7%)	36 (9.3%)	
LOS (days), median (IQR)	10 (8, 11)	10 (8, 12)	0.255
Admission NIHSS, median (IQR)	10.8 (9.0, 13.0)	14.3 (12.0, 16.2)	< 0.001
Admission GCS, median (IQR)	10 (9, 12)	10 (8, 12)	0.420
Admission mRs, 0 ~ 2 score, n (%)			0.225
No	173 (44.7%)	75 (19.4%)	
Yes	105 (27.1%)	34 (8.8%)	
FBG ≥ 11.0 mmol/L, n (%), n (%)			0.731
No	236 (61%)	91 (23.5%)	
Yes	42 (10.9%)	18 (4.7%)	
Hemoglobin (g/dL), median (IQR)	13.3 (11.9, 15.0)	13 (12.1, 15.3)	0.728

Cre (mg/dL), median (IQR)	1.2 (1.0, 1.5)	1.2 (0.9, 1.5)	0.765
Hcy (μmol/L), median (IQR)	17 (14, 20)	17 (14, 20)	0.831
UA (μmol/L), median (IQR)	357.5 (333.0, 462.5)	385.0 (320.0, 463.0)	0.477
D-D (mg/L), median (IQR)	1.5 (1.2, 1.8)	1.6 (1.2, 1.9)	0.339
hs-CRP (mg/L), median (IQR)	12.4 (8.3, 15.2)	14.2 (9.8, 17.9)	< 0.001
TG (mmol/L), median (IQR)	2.03 (1.84, 2.10)	1.98 (1.75, 2.16)	0.422
TC (mmol/L), median (IQR)	4.70 (4.20, 5.00)	4.70 (4.20, 5.20)	0.183
LDL-C (mmol/L), median (IQR)	2.90 (2.60, 3.10)	3.00 (2.70, 3.30)	0.003
HDL-C (mmol/L), median (IQR)	1.20 (1.08, 1.33)	1.21 (1.11, 1.34)	0.284
SAA-T1 (mg/L), median (IQR)	36.0 (33.1, 39.0)	56.2 (34.5, 77.3)	< 0.001
SAA-T2 (mg/L), median (IQR)	40.1 (31.2, 45.1)	74.6 (56.0, 92.7)	< 0.001
SAA-T3 (mg/L), median (IQR)	42.8 (33.0, 51.4)	69.4 (50.6, 78.3)	< 0.001
30-day mortality, n (%)			< 0.001
No	248 (64.1%)	73 (18.9%)	
Yes	30 (7.8%)	36 (9.3%)	

AIS, acute ischemic stroke; VAP, ventilator-associated pneumonia; IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TOAST, Trial of ORG 10172 in acute stroke treatment; TICI, thrombolysis in cerebral infarction; LOS, length of stay; NIHSS, national Institute of Health stroke scale; GCS, Glasgow Coma Scale; mRs, modified Rankin Scale; FBG, fasting blood glucose; Cre, creatinine; Hcy, homocysteine; UA, uric acid; D-D, D-Dimer; hs-CRP, high-sensitivity C reactive protein; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SAA, serum amyloid A; T1, pre-operation; T2, 48 hours post-mechanical ventilation; T3, 96 hours post-mechanical ventilation.

Table 2. Univariate and multivariate analysis to identify VAP-related risk factors in patients with AIS.

Characteristics	Total(N)	Univariate analysis		Multivariate analysis	
		Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Age (years)	387	1.078 (1.042 – 1.115)	< **0.001**	1.096 (1.032 – 1.164)	**0.003**
Time of mechanical ventilation (days)	387				
≤ 2	260	Reference		Reference	
> 2	127	3.081 (1.940 – 4.891)	< **0.001**	3.990 (1.721 – 9.247)	**0.001**
DBP (mmHg)	387	1.337 (1.215 – 1.473)	< **0.001**	1.174 (1.030 – 1.339)	**0.017**
Admission NIHSS	387	1.392 (1.276 – 1.517)	< **0.001**	1.309 (1.145 – 1.497)	< **0.001**
hs-CRP (mg/L)	387	1.111 (1.058 – 1.166)	< **0.001**	1.143 (1.045 – 1.250)	**0.004**
TC (mmol/L)	387	1.577 (1.133 – 2.195)	**0.007**	2.297 (1.221 – 4.320)	**0.010**
LDL-C (mmol/L)	387	3.371 (2.001 – 5.678)	< **0.001**	2.225 (0.838 – 5.910)	0.109
SAA-T2 (mg/L)	387	1.103 (1.080 – 1.125)	< **0.001**	1.104 (1.076 – 1.132)	< **0.001**

AIS, acute ischemic stroke; VAP, ventilator-associated pneumonia; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C reactive protein; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; SAA, serum amyloid A.

Table 3. ROC analysis was performed to evaluate the predictive efficiency of risk factors for VAP in AIS patients.

Variables	AUC (95% CI)	Cut-off value	Sensitivity	Specificity	Accuracy
Age (years)	0.639 (0.576 – 0.701)	71.500	0.706	0.514	0.568
Time of mechanical ventilation (days)	0.629 (0.576 – 0.683)	0.500	0.514	0.745	0.680
DBP (mmHg)	0.724 (0.672 – 0.776)	80.500	0.963	0.388	0.550
Admission NIHSS	0.755 (0.698 – 0.812)	13.001	0.651	0.755	0.726
hs-CRP (mg/L)	0.617 (0.552 – 0.683)	16.100	0.385	0.827	0.703
TC (mmol/L)	0.543 (0.477 – 0.610)	5.550	0.156	0.982	0.749
SAA-T2 (mg/L)	0.885 (0.842 – 0.928)	51.11	0.817	0.924	0.894

ROC, receiver operator characteristic curve; CI; confidence interval; AIS, acute ischemic stroke; VAP, ventilator-associated pneumonia; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C reactive protein; TC, total cholesterol; SAA, serum amyloid A.

Table 4. ROC analysis was performed to evaluate the predictive efficiency of different models for VAP in AIS patients.

Variables	AUC (95% CI)	Cut-off value	Sensitivity	Specificity	Accuracy
[$]Model1	0.889 (0.853 – 0.924)	-1.162	0.853	0.788	0.806
[&]Model2	0.961 (0.942 – 0.980)	-0.687	0.862	0.928	0.910
P value	< 0.001				

[$]Model1 was composed with 6 risk factors, including age, Time of mechanical ventilation, DBP, admission NIHSS, hs-CRP, and TC;

[&]Model2 was combined with Model1 and SAA-T2.

ROC, receiver operator characteristic curve; CI; confidence interval; AIS, acute ischemic stroke; VAP, ventilator-associated pneumonia; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C reactive protein; TC, total cholesterol; SAA, serum amyloid A.

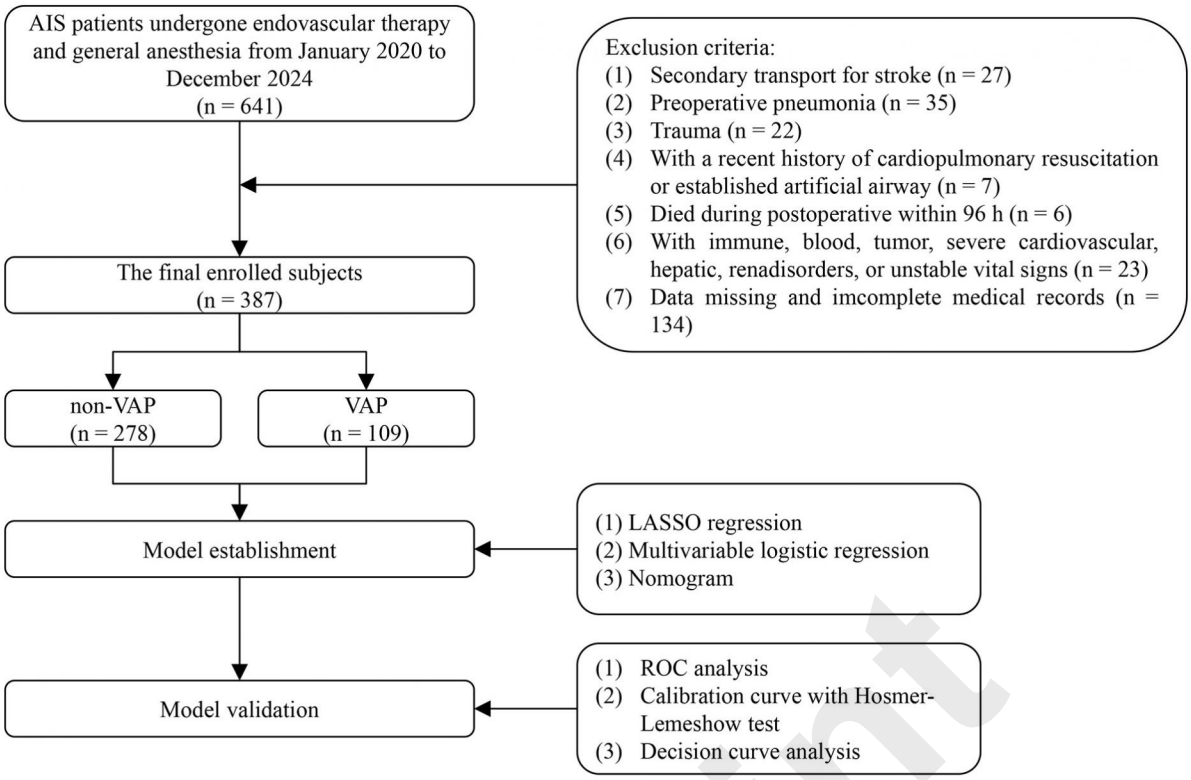

Figure 1. Flowchart of participant enrollment, model development, and validation.

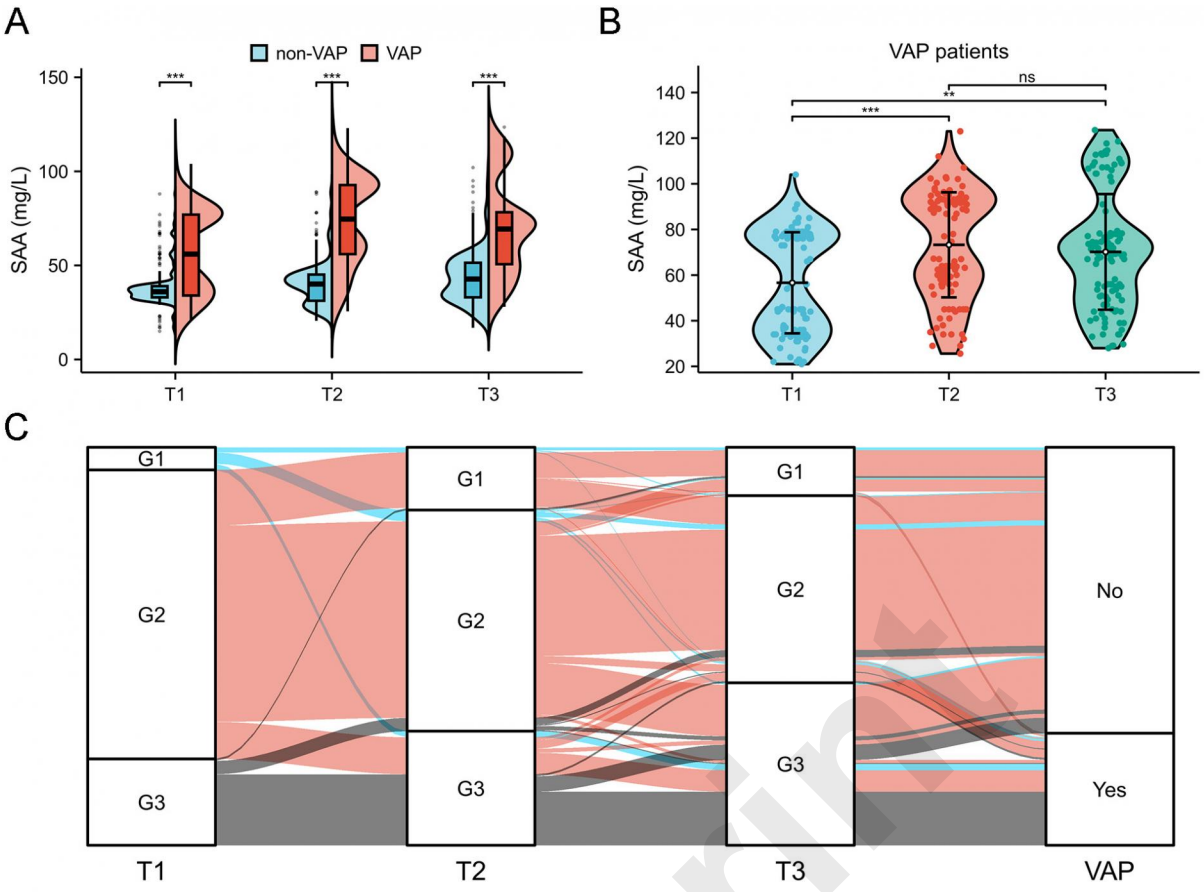

Figure 2. SAA level associated with VAP in AIS patients.

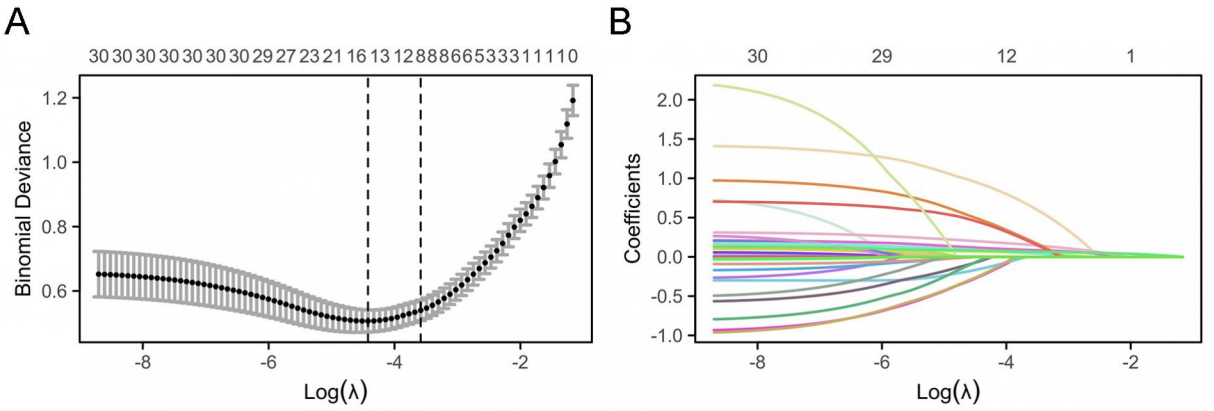

Figure 3. Screening of VAP-related risk factors in AIS patients with LASSO.

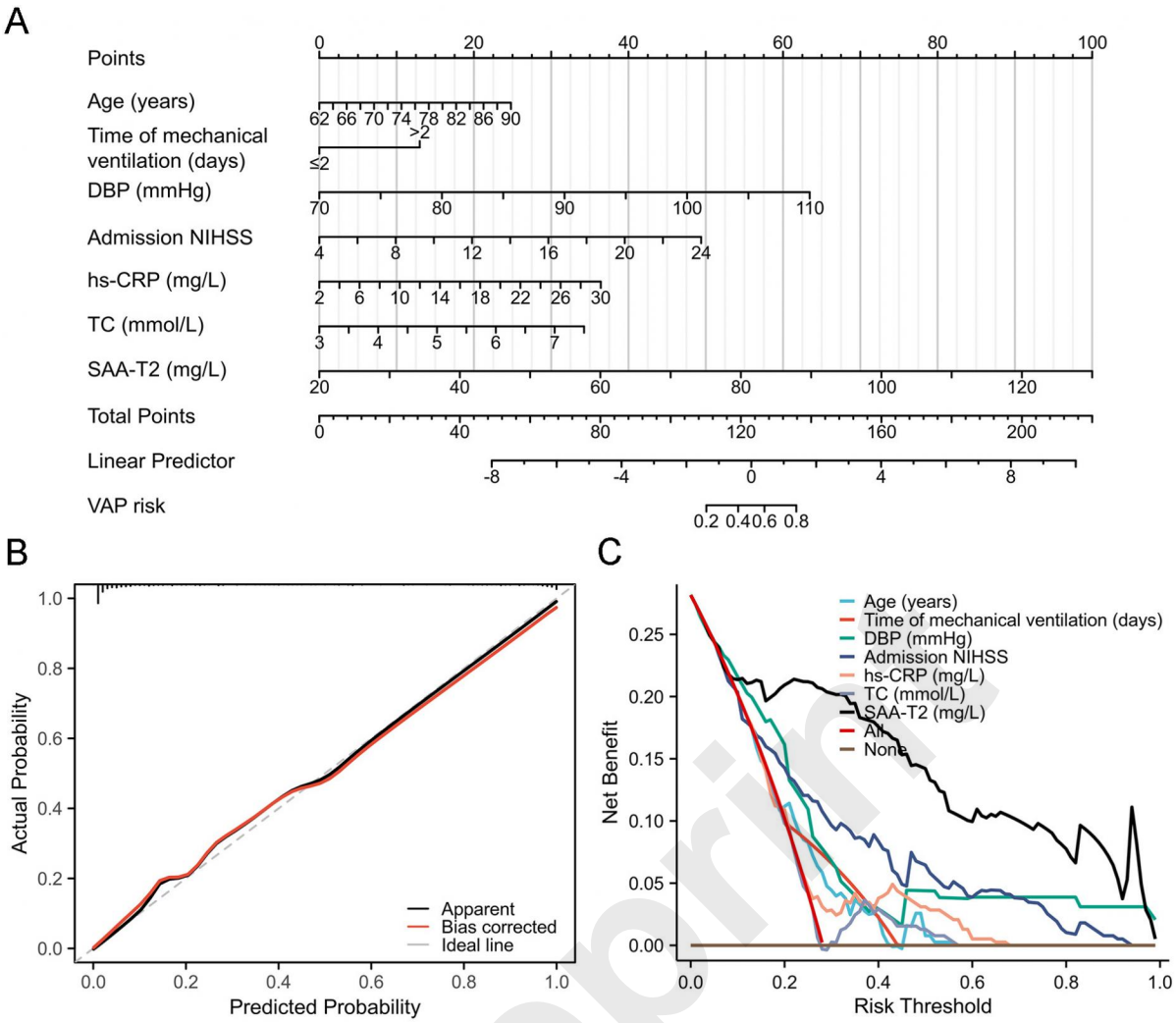

Figure 4. Establishment of a nomogram for predicting VAP of patients with AIS.

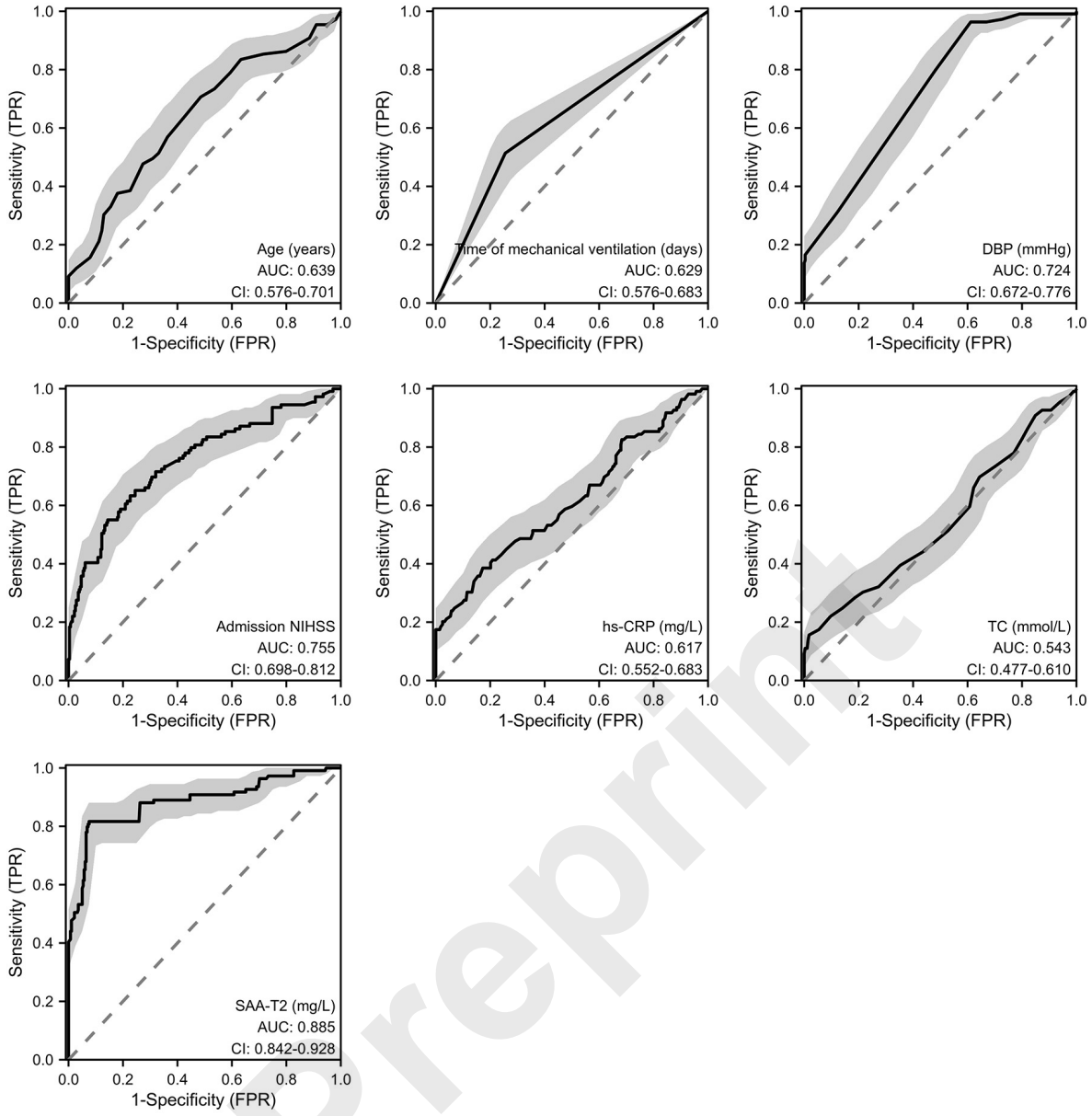

Figure 5. ROC analysis was performed to evaluate the predictive efficiency of risk factors for VAP in AIS patients.

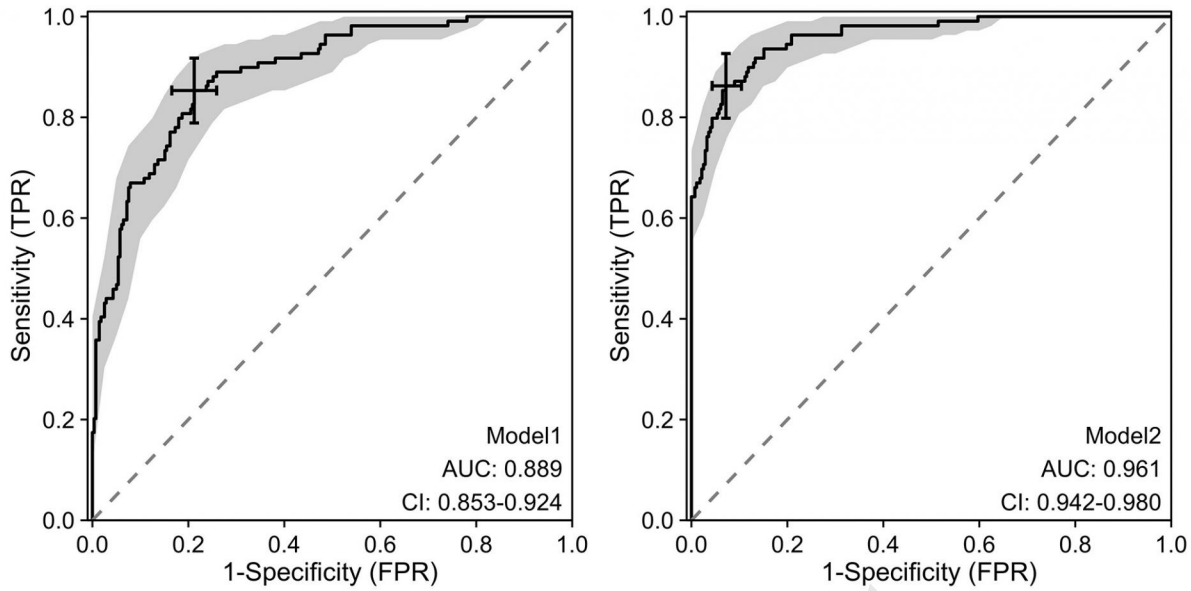

Figure 6. ROC analysis was performed to evaluate the predictive efficiency of combined models for VAP in AIS patients.

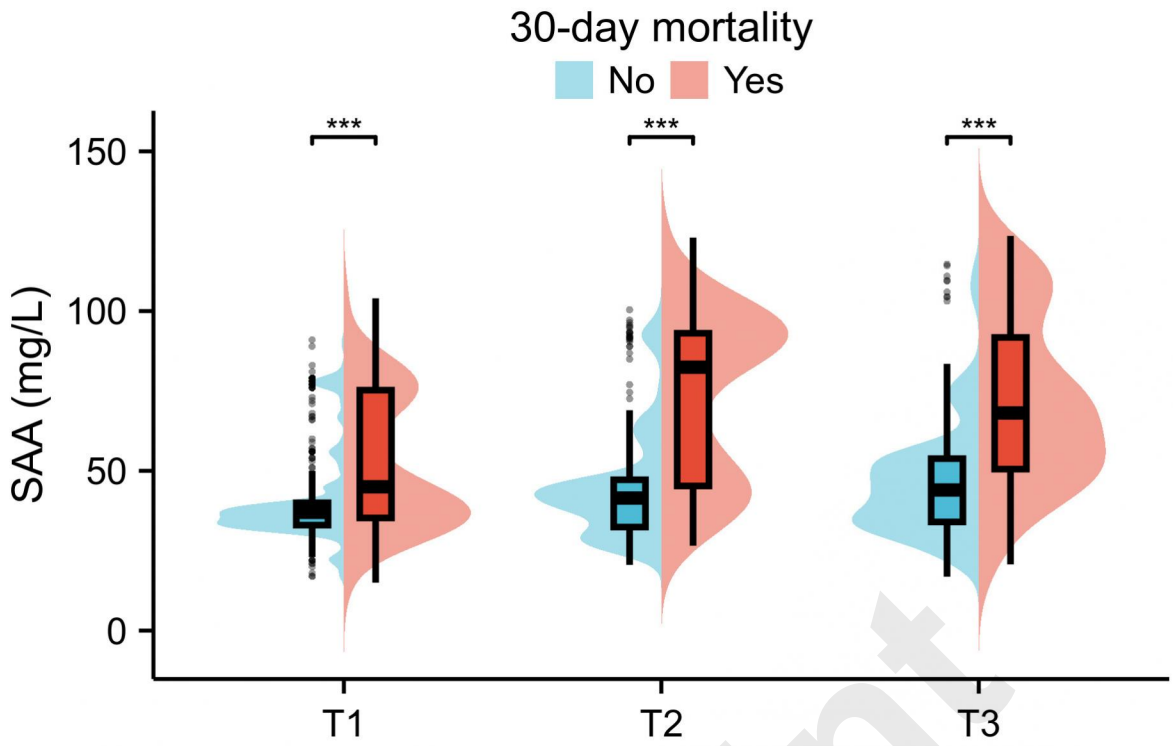

Figure 7. SAA level associated with poor prognosis of AIS patients.