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A nomogram based on nutritional status and A²DS² score for predicting stroke-associated pneumonia in acute ischemic stroke patients with type 2 diabetes mellitus: A retrospective study

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Background: Stroke-associated pneumonia (SAP) commonly complicates acute ischemic stroke (AIS) and significantly worsens outcomes. Type 2 diabetes mellitus (T2DM) may contribute to malnutrition, impair innate immunity function, and increase the probability of SAP occurrence in AIS patients. We aimed to determine early predictors of SAP in AIS patients with T2DM and to construct a nomogram specifically for predicting SAP in this population by combining the A²DS² score with available nutrition-related parameters.

Methods: A total of 1,330 consecutive AIS patients with T2DM were retrospectively recruited. The patients were randomly allocated to the training ($n = 887$) and validation groups ($n = 443$). Univariate and multivariate binary logistic regression analyses were applied to determine the predictors of SAP in the training group. A nomogram was established according to the identified predictors. The areas under the receiver operating characteristic curve (AUROC) and calibration plots were performed to assess the predictive values of the nomogram. The decision curve was applied to evaluate the net benefits of the nomogram.

Results: The incidence of SAP was 9% and 9.7% in the training and validation groups, respectively. The results revealed that the A²DS² score, stroke classification, Geriatric Nutritional Risk Index, hemoglobin, and fast blood glucose were independent predictors for SAP. A novel nomogram, A²DS²-Nutrition, was constructed based on these five predictors. The AUROC for A²DS²-Nutrition (0.820, 95% CI: 0.794–0.845) was higher than the A²DS² score (0.691, 95% CI: 0.660–0.722) in the training group. Similarly, it showed a better predictive performance than the A²DS² score [AUROC = 0.864 (95% CI: 0.828–0.894) vs. AUROC = 0.763 (95% CI: 0.720–0.801)] in the

validation group. These results were well calibrated in the two groups. Moreover, the decision curve revealed that the A²DS²-Nutrition provided an additional net benefit to the AIS patients with T2DM compared to the A²DS² score in both groups.

Conclusion: The A²DS² score, stroke classification, Geriatric Nutritional Risk Index, hemoglobin, and fast blood glucose were independent predictors for SAP in AIS patients with T2DM. Thus, the proposed A²DS²-Nutrition may be a simple and reliable prediction model for SAP occurrence in AIS patients with T2DM.

KEYWORDS

stroke-associated pneumonia, nutritional status, A²DS² score, acute ischemic stroke, type 2 diabetes mellitus

Introduction

Stroke-associated pneumonia (SAP) is a spectrum of pneumonia complications that develop in non-ventilated patients following a stroke (1). The incidence of SAP was estimated to be 12.3% [95% confidential interval (CI), 11%–13.6%] (2). SAP significantly lengthens hospitalization and raises hospital costs (3–5). Furthermore, it is independently associated with worse functional outcomes and increased mortality rates (5, 6).

Diabetes was discovered to be related to SAP (7). Moreover, diabetes was found in approximately 33% of ischemic stroke patients and was closely associated with poor outcomes in this population (8). Patients with type 2 diabetes mellitus (T2DM) were more susceptible to community-acquired pneumonia (relative risk = 1.64, 95% CI, 1.55–1.73) than the non-T2DM in a meta-analysis incorporating about 15 million people (9). A plausible explanation is that hyperglycemia impair immunological function in T2DM patients (10). Furthermore, a significant malnutrition prevalence was found in hospitalized older patients with T2DM (11), due to gastroparesis, diet changes, and chronic kidney disease (12). Malnutrition is an issue commonly related to secondary immune deficiency and infection risk (13). Therefore, it is reasonable to pay more attention to the risk of SAP in acute ischemic stroke (AIS) patients with T2DM.

SAP is considered a potentially modifiable complication affecting stroke prognosis. Thus, identifying vulnerable patients

is crucial to tailor monitoring and prophylactic strategies. Efforts have been made to establish prediction SAP scales, including the A²DS², the PANTHERS, the ISAN, and the AIS-APS score (14). The A²DS² score is the most extensively utilized risk scale in practice. It has had a moderate predictive accuracy for SAP (AUROC = 0.85, 95% CI, 0.82–0.88) (15). In addition, some simple nutrition-related biomarkers, such as hyperglycemia (16) and serum albumin (17), had good predictive value for SAP. However, no existing research has been made to specifically predict SAP in patients with comorbidity of AIS and T2DM. There is also no prediction scale that takes nutritional risk status into account as an important factor.

In the present study, we retrospectively evaluated the relevance of the A²DS² score with SAP in AIS patients with T2DM. Furthermore, we attempted to establish an individualized nomogram for discerning SAP in these patients by combining the A²DS² score with simple nutrition-related biomarkers.

Materials and methods

Patients selection

This was a retrospective study conducted at the Peking University People's Hospital (PKUPH) between January 2015 and September 2021. Consecutive AIS patients with T2DM who were admitted within 24 h of symptom onset were enrolled in our cohort. All participants met the WHO criteria for the diagnosis of AIS (18). The diagnosis of T2DM was based on the American Diabetes Association diagnostic criteria (19) or clear T2DM history. The exclusion criteria included the following: (1) age < 18 years; (2) diagnosis of transient ischemic attacks (TIA) or cerebral hemorrhage; (3) active pulmonary or other sites infection within the last 14 days; (4) history of severe hepatic diseases, hematological malignancy, or immunosuppressant

Abbreviations: SAP, stroke-associated pneumonia; AIS, acute ischemic stroke; T2DM, type 2 diabetes mellitus; AUROC, areas under the receiver operating characteristic curve; CI, confidence interval; OR, odds ratio; PKUPH, Peking University People's Hospital; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; LACI, lacunar infarct; OSCP, Oxfordshire Community Stroke Project; BMI, body mass index; FBG, fast blood glucose; ALB, albumin; NLR, neutrophil to lymphocyte ratio; GNRI, Geriatric Nutritional Risk Index; CXR, chest X-ray.

treatment; (5) recent history of major trauma or surgery, and (6) incomplete medical records. This study was approved by the ethics committee at PKUPH and conducted in accordance with the Declaration of Helsinki.

Data collection

The demographic and clinical data were recorded at the time of admission, including age, sex, height, weight, stroke classification, National Institutes of Health Stroke Scale (NIHSS) score at admission, hypertension, dyslipidemia, hyperuricemia, atrial fibrillation, previous myocardial infarction, chronic heart failure, previous stroke, dementia, dysphasia, chronic obstructive pulmonary disease, chronic kidney disease, malignancy, smoking status, and drinking status. AIS was classified into four subtypes, including total anterior circulation infarct, partial anterior circulation infarct, posterior circulation infarct, and lacunar infarct (LACI), according to the Oxfordshire Community Stroke Project (OCSP) classification system (20). Body mass index (BMI) was defined as the weight (kg) divided by height square (m^2). As previously reported, the A^2DS^2 score was determined by summing up the points of the corresponding risk factors: 3 for age ≥ 75 years, 1 for atrial fibrillation, 2 for dysphasia, 1 for male, 0 for NIHSS 0–4, 3 for NIHSS 5–15, and 5 for NIHSS ≥ 16 (21). The following laboratory parameters were collected within 24 h of admission: hemoglobin, neutrophils, lymphocyte, platelet, fast blood glucose (FBG), glycosylated hemoglobin, serum creatinine, estimated glomerular filtration rate, serum albumin (ALB), total cholesterol, total glyceride, high-density lipoprotein, and low-density lipoprotein. Neutrophil to lymphocyte ratio (NLR) was defined as the neutrophil count ($10^9/L$) divided by lymphocyte count ($10^9/L$). The Geriatric Nutritional Risk Index (GNRI) formula was as follows: $GNRI = [1.489 \times ALB (g/L)] + [41.7 \times \text{current weight (kg)}/\text{ideal body weight (kg)}]$ (22). Ideal weight was calculated based on the Lorentz equations: for men: ideal body weight = height (cm) – 100 – [height (cm) – 150]/4; for women: ideal body weight = height (cm) – 100 – [height (cm) – 150]/2. GNRI scores > 98 , 92–98, 82–91, and < 82 were considered to indicate absent, low, moderate, and severe malnutrition risk, respectively (22).

Outcome definition

SAP was defined as pneumonia complicating the first week after AIS onset in non-ventilated patients (1). In our study, clinically suspected SAP was diagnosed based on the modified Centers for Disease Control and Prevention

criteria, according to the clinical symptoms and laboratory tests (23). Definite SAP was confirmed by typical chest X-ray (CXR) changes within 48 h of antibiotic initiation (1). However, only 36% of clinically suspected SAP manifested typical pneumonia findings on an initial CXR (1). Hence, in clinical practice, pulmonary computed tomography was undertaken within 48 h after consent following the suspicion of pneumonia, albeit with a with normal CXR appearance (24).

Statistical analysis

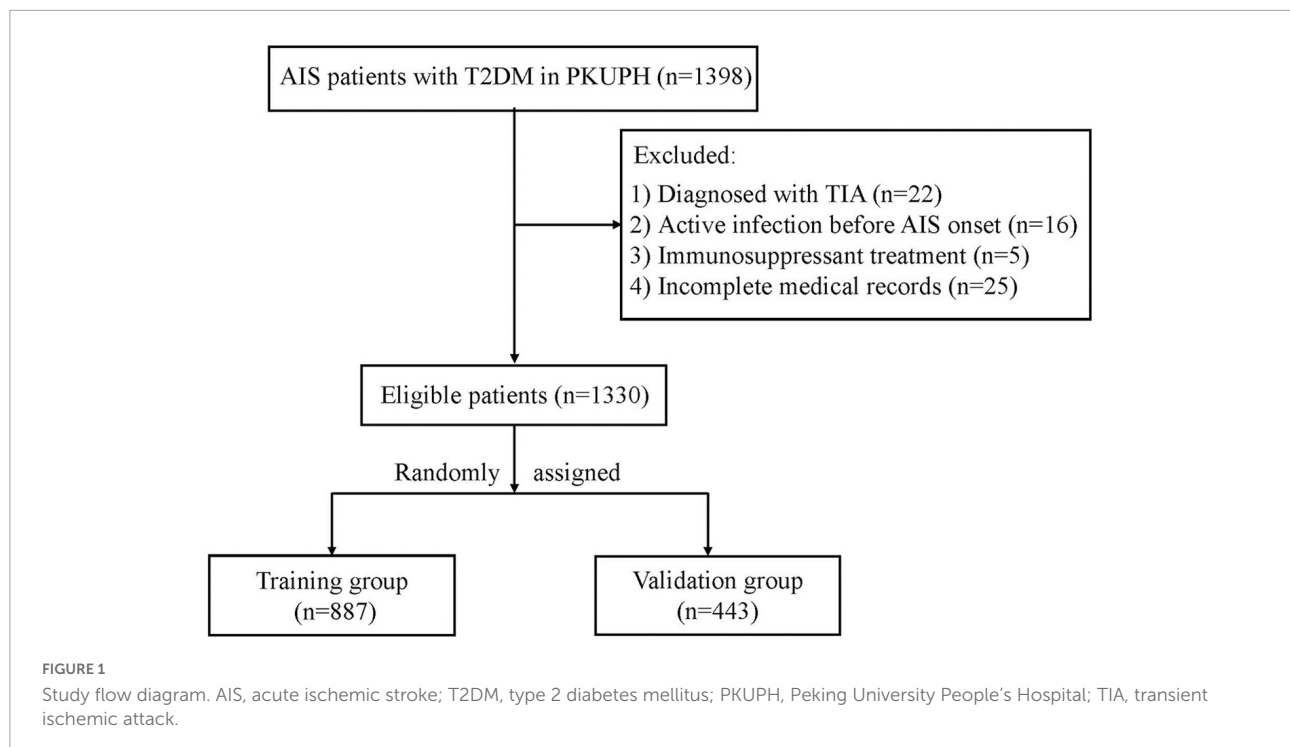
IBM SPSS Statistics version 22.0 (IBM Corp.) and R project for Statistical Computer version 4.1.2 were applied for the statistical analyses. A 2-sided P -value < 0.05 was considered statistically significant. Continuous variables were presented as mean with the standard deviation if normally distributed and median with interquartile range otherwise. The t -test and Mann–Whitney U test were performed for comparison among the groups in continuous variables. The Fisher's exact test and Pearson's Chi-square test were employed to explore differences in the categorical variables.

Random number generator of SPSS was applied for random grouping of the participants. Two-thirds of the patients were randomly allocated to the training group to establish a nomogram, and the remaining were allocated to the validation group. Univariate logistic regression was applied to identify the potential variables associated with SAP. Then, the variables were included in the multivariate logistic regression when the P -value < 0.05 . The results of multivariate regression were visualized as a forest plot. A nomogram was constructed based on the multivariate logistic regression. The nomogram was compared with the A^2DS^2 score by performing the area under the receiver operating characteristic curve (AUROC). The calibration plots were used to assess the performance of the nomogram with 1,000 bootstraps resamples. Moreover, the decision curve was applied to evaluate the net benefits of the nomogram.

Results

Clinical characteristics of the study cohort

As shown in the flow chart of **Figure 1**, 1,398 T2DM patients with AIS attended PKUPH between January 2015 and September 2021. 22 patients diagnosed with TIA, 16 with the active infection before stroke onset (3 with



sepsis and 13 with urinary tract infections), 5 receiving immunosuppressant treatment, and 25 with incomplete medical records were excluded from the cohort. Two-thirds of the patients ($n = 887$) were allocated to the training group, with the remaining ($n = 443$) allocated to the validation group. In addition to age, there was no significant difference in baseline demographic and clinical variables between the two groups (Table 1). SAP incidence rates were similar in both groups (9% vs. 9.7%, $P = 0.683$).

Baseline characteristics of patients in the training group stratified by SAP

Patients with SAP ($n = 80$) were older (71.3 ± 12.2 vs. 66.7 ± 11.8 years) and had higher NIHSS [5.5 (3.0–11.3) vs. 3.0 (2.0–5.0)], A^2DS^2 scores [4.0 (1.0–6.0) vs. 1.0 (1.0–4.0)], and GNRI (91.7 ± 11.4 vs. 101.6 ± 11.0) than those without SAP ($n = 807$). Patients diagnosed with SAP showed lower BMI (21.1 ± 3.5 vs. 23.6 ± 4.6 kg/m²) and had higher incidence of non-LACI (76.3% vs. 46.6%), atrial fibrillation (13.8% vs. 6.4%), previous myocardial infarction (16.3% vs. 5.9%), and dysphagia (11.6% vs. 32.5%) than its counterparts. For laboratory features, the levels of hemoglobin (117.9 ± 29.0 vs. 135.3 ± 17.4 g/L), lymphocyte [1.1 (0.7–1.5) vs. 1.6 (1.2–2.0) $\times 10^9/L$], and ALB [35.3 (31.8–38.2) vs. 39.0 (36.5–41.0) g/L] were lower in the SAP group than in the non-SAP group. In addition, the levels

of neutrophils [5.3 (3.8–7.0) vs. 4.0 (3.2–5.1) $\times 10^9/L$], NLR [4.4 (2.0–6.9) vs. 2.5 (1.9–3.5) $\times 10^9/L$], and FBG [9.8 (8.0–15.6) vs. 7.4 (6.1–10.0) $\times 10^9/L$] were higher in the SAP group when compared with its counterparts (Table 2).

Development of a predictive nomogram for SAP

According to the univariate logistic regression analysis, fifteen factors were significantly correlated with SAP. They were age, BMI, OCSF classification, NIHSS score, A^2DS^2 score, Geriatric Nutritional Risk Index (GNRI), atrial fibrillation, previous myocardial infarction, dysphagia, hemoglobin, neutrophils, lymphocyte, NLR, FBG, and ALB (Table 2). Age, atrial fibrillation, dysphagia, and NIHSS were not included in the multivariate regression analysis since they were parts of the A^2DS^2 score. In addition, neutrophils and lymphocytes, and BMI and ALB, were excluded from subsequent analysis because they were the main elements of the NLR and GNRI formula separately. Finally, the remaining seven factors were incorporated into the multivariate logistic regression. The results revealed that A^2DS^2 score, OCSF classification (non-LACI), GNRI, hemoglobin, and FBG were independent predictors for SAP (Figure 2). All VIF values were ≤ 1.15 , indicating low collinearity among the variables. Based on these independent predictors, a nomogram, A^2DS^2 -Nutrition,

TABLE 1 Demographic and clinical variables of patients.

Variable	All cases (n = 1330)	Training Group (n = 887)	Validation Group (n = 443)	P-value
Male, n (%)	868 (65.3)	589 (66.4)	279 (63.0)	0.216
Age (years), mean (SD)	67.7 (12.0)	67.1 (11.9)	68.8 (12.2)	0.016
SAP, n (%)	123 (9.2)	80 (9.0)	43 (9.7)	0.683
BMI (kg/m ²), mean (SD)	23.3 (4.6)	23.4 (4.6)	23.2 (4.7)	0.439
OCSP				
TACI, n (%)	105 (7.9)	70 (7.9)	35 (7.9)	0.995
PACI, n (%)	295 (22.2)	190 (21.4)	105 (23.7)	0.345
POCI, n (%)	261 (19.6)	177 (20.0)	84 (19.0)	0.667
LACI, n (%)	669 (50.3)	450 (50.7)	219 (49.4)	0.656
NIHSS at admission, median (IQR)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	0.497
A ² DS ² , median (IQR)	1.0 (1.0–4.0)	1.0 (1.0–4.0)	1.0 (1.0–4.0)	0.913
GNRI, mean (SD)	100.6 (11.5)	100.7 (11.4)	100.3 (11.8)	0.522
Smoking, n (%)	511 (38.4)	354 (39.9)	157 (35.4)	0.114
Drinking, n (%)	322 (24.2)	210 (23.7)	112 (25.3)	0.519
Hypertension, n (%)	1,019 (78.4)	688 (77.6)	331 (74.7)	0.248
Dyslipidemia, n (%)	914 (68.7)	620 (69.9)	294 (66.3)	0.190
Hyperuricemia, n (%)	94 (7.1)	65 (7.3)	29 (6.5)	0.600
Atrial fibrillation, n (%)	97 (7.3)	63 (7.1)	34 (7.7)	0.705
Previous MI, n (%)	85 (6.4)	61 (6.9)	24 (5.4)	0.305
CHF, n (%)	16 (1.2)	8 (0.9)	8 (1.8)	0.154
Previous stroke, n (%)	112 (8.4)	76 (8.6)	36 (8.1)	0.785
COPD, n (%)	17 (1.2)	12 (1.4)	5 (1.1)	0.732
CKD, n (%)	45 (3.4)	33 (3.7)	12 (2.7)	0.336
Malignancy, n (%)	69 (5.2)	43 (4.8)	26 (5.9)	0.429
Dementia, n (%)	51 (3.8)	35 (3.9)	16 (3.6)	0.765
Dysphagia, n (%)	175 (13.2)	120 (13.5)	55 (12.4)	0.571
Hemoglobin (g/L), mean (SD)	133.4 (19.4)	133.7 (19.4)	132.8 (19.3)	0.413
Neutrophils (× 10 ⁹ /L), median (IQR)	4.1 (3.3–5.4)	4.1 (3.3–5.4)	4.3 (3.4–5.4)	0.199
NLR, median (IQR)	2.5 (1.9–3.7)	2.5 (1.9–3.7)	2.7 (2.0–3.9)	0.087
Lymphocyte (× 10 ⁹ /L), median (IQR)	1.6 (1.2–2)	1.6 (1.2–2.0)	1.6 (1.2–1.9)	0.517
Platelet (× 10 ⁹ /L), median (IQR)	195.0 (159.3–232.0)	195.0 (159.0–232.0)	195.0 (161.0–232.0)	0.729
FBG (mmol/L), median (IQR)	7.7 (6.2–10.3)	7.6 (6.2–10.4)	7.8 (6.2–9.8)	0.550
HbA1c (%), median (IQR)	7.7 (6.8–9.0)	7.7 (6.8–9.0)	7.6 (6.8–9.0)	0.832
SCR (μmol/L), median (IQR)	70.0 (58.3–86)	71.0 (59.0–87.0)	69.0 (58.0–86.0)	0.850
eGFR (ml/min*1.73m ²), median (IQR)	88.3 (71.4–98.4)	88.6 (72.1–98.3)	87.4 (69.6–98.6)	0.313
ALB (g/L), median (IQR)	38.7 (35.9–40.9)	38.8 (36.0–40.9)	38.5 (35.6–41.1)	0.547
TC (mmol/L), median (IQR)	4.2 (3.4–5.1)	4.2 (3.4–5.1)	4.3 (3.5–5.2)	0.537
TG (mmol/L), median (IQR)	1.5 (1.1–2.1)	1.5 (1.2–2.1)	1.5 (1.1–2.0)	0.344
HDL (mmol/L), median (IQR)	1.0 (0.8–1.2)	1.0 (0.8–1.1)	1.0 (0.8–1.2)	0.720
LDL (mmol/L), median (IQR),	2.6 (2.0–3.3)	2.6 (2.0–3.3)	2.6 (2.0–3.4)	0.483

SAP, stroke-associated pneumonia; SD, standard deviation; IQR, interquartile range; BMI, body mass index; OCSP, Oxfordshire Community Stroke Project; TACI, total anterior circulation infarction; PACI, partial anterior circulation infarction; POCI, posterior circulation infarction; LACI, lacunar circulation infarction; NIHSS, National Institutes of Health Stroke Scale; GNRI, Geriatric Nutritional Risk Index; MI, myocardial infarction; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; NLR, neutrophil-to-lymphocyte ratio; FBG, fast blood glucose; HbA1c, glycosylated hemoglobin; SCR, serum creatinine clearance; eGFR, estimated glomerular filtration rate; ALB, albumin; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

Bold values mean P-value < 0.05.

was constructed to predict the probability of SAP in AIS patients with T2DM (Figure 3). The A²DS²-Nutrition assigned a probability (5%–95%) of SAP occurrence. Each

risk factor was assigned a point based on the nomogram. The total points were calculated by adding the corresponding scores on each variable's scale point. The probability of

TABLE 2 Univariate regression analysis of SAP in the training group.

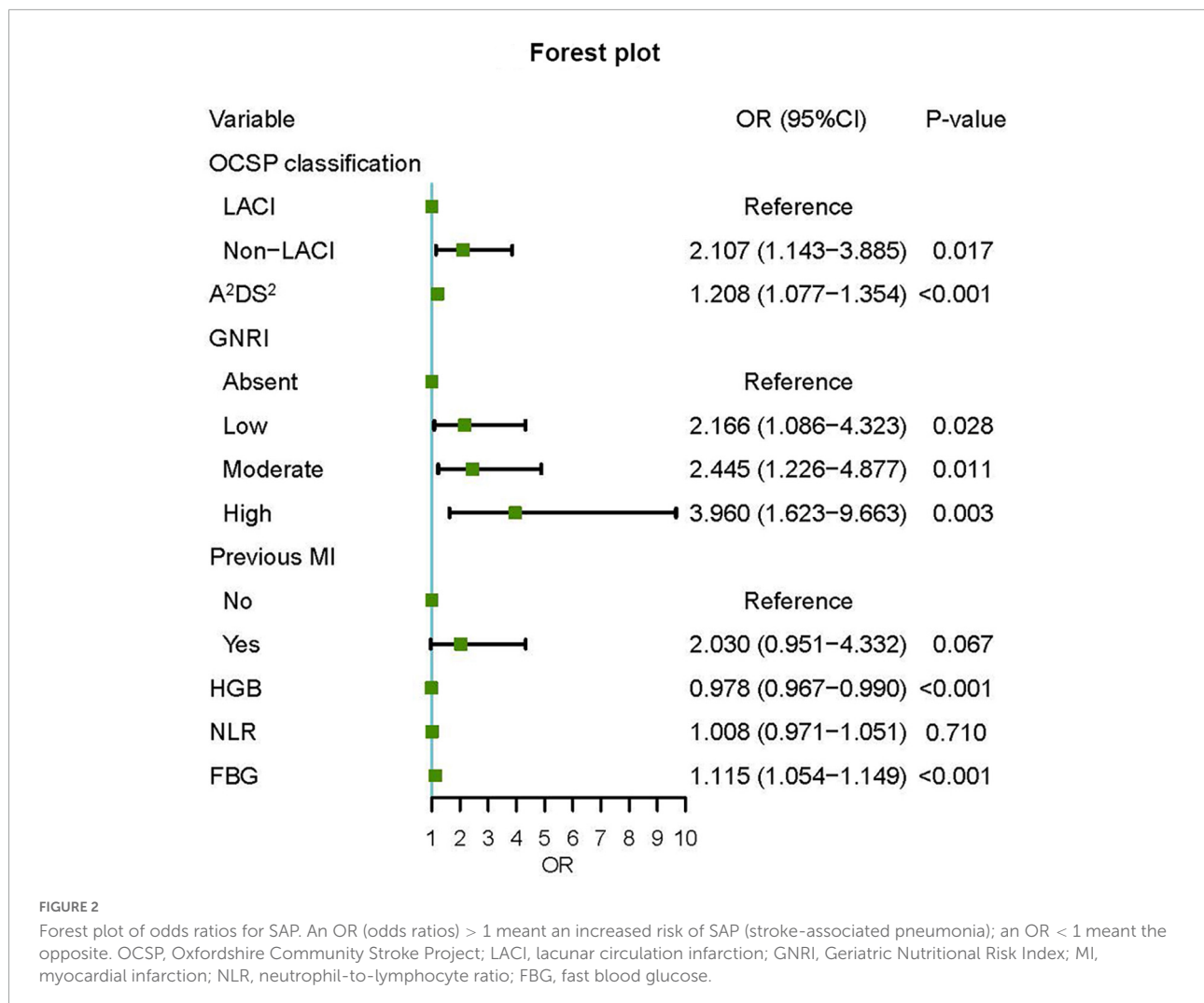
Variable	Non-SAP group (N = 807)	SAP group (N = 80)	P-value	OR (95% CI)	P-value
Male, n (%)	540 (66.9)	49 (61.3)	0.306	0.782 (0.4870–1.254)	0.307
Age (years), mean (SD)	66.7 (11.8)	71.3 (12.2)	0.001	1.035 (1.014–1.056)	0.001
BMI (kg/m ²), mean (SD)	23.6 (4.6)	21.1 (3.5)	< 0.001	0.857 (0.804–0.911)	< 0.001
OCSP					
LACI, n (%)	431 (53.4)	19 (23.8)		Reference	
Non-LACI, n (%)	376 (46.6)	61 (76.3)	< 0.001	3.680 (2.159–6.272)	< 0.001
NIHSS at admission, median (IQR)	3.0 (2.0–5.0)	5.5 (3.0–11.3)	< 0.001	1.072 (1.045–1.099)	< 0.001
A ² DS ² , median (IQR)	1.0 (1.0–4.0)	4.0 (1.0–6.0)	< 0.001	1.368 (1.242–1.507)	< 0.001
GNRI, mean (SD)	101.6 (11.0)	91.7 (11.4)	< 0.001	0.919 (0.897–0.940)	< 0.001
Absent malnutrition risk, n (%)					
Low malnutrition risk, n (%)	524 (64.9)	24 (30.0)		Reference	
Moderate malnutrition risk, n (%)	138 (17.1)	17 (21.3)		2.812 (1.462–5.410)	0.002
High malnutrition risk, n (%)	117 (14.5)	25 (31.3)		4.877 (2.675–8.893)	< 0.001
Smoking, n (%)	27 (3.3)	15 (18.8)		12.681 (5.950–27.029)	< 0.001
Drinking, n (%)	323 (40.0)	31 (38.8)	0.824	0.948 (0.592–1.519)	0.824
Hypertension, n (%)	190 (23.5)	20 (25.0)	0.770	1.083 (0.636–1.842)	0.770
Dyslipidemia, n (%)	628 (77.8)	60 (75.0)	0.564	0.855 (0.502–1.457)	0.565
Hyperuricemia, n (%)	560 (69.4)	60 (75.0)	0.297	1.323 (0.781–2.243)	0.298
Atrial fibrillation, n (%)	61 (7.6)	4 (5.0)	0.402	0.644 (0.228–1.819)	0.406
Previous MI, n (%)	52 (6.4)	11 (13.8)	0.015	2.315 (1.155–4.644)	0.018
CHF, n (%)	48 (5.9)	13 (16.3)	0.001	3.068 (1.583–5.947)	< 0.001
Previous stroke, n (%)	7 (0.9)	1 (1.3)	0.730	1.447 (0.176–11.91)	0.731
COPD, n (%)	70 (8.7)	6 (7.5)	0.720	0.854 (0.359–2.032)	0.721
CKD, n (%)	9 (1.1)	3 (3.8)	0.086	3.455 (0.916–13.028)	0.067
Malignancy, n (%)	27 (3.3)	6 (7.5)	0.110	2.342 (0.937–5.855)	0.069
Dementia, n (%)	36 (4.4)	7 (8.8)	0.099	2.054 (0.883–4.778)	0.095
Dysphagia, n (%)	30 (3.7)	5 (6.3)	0.235	1.727 (0.651–4.582)	0.273
Hemoglobin (g/L), mean (SD)	94 (11.6)	26 (32.5)	< 0.001	3.652 (2.182–6.112)	< 0.001
Neutrophils ($\times 10^9/L$), median (IQR)	135.3 (17.4)	117.9 (29.0)	< 0.001	0.963 (0.953–0.973)	< 0.001
NLR, median (IQR)	4.0 (3.2–5.1)	5.3 (3.8–7.0)	< 0.001	1.137 (1.052–1.229)	0.001
Lymphocyte ($\times 10^9/L$), median (IQR)	2.5 (1.9–3.5)	4.4 (2.0–6.9)	< 0.001	1.089 (1.047–1.132)	< 0.001
Platelet ($\times 10^9/L$), median (IQR)	1.6 (1.2–2.0)	1.1 (0.7–1.5)	< 0.001	0.293 (0.189–0.454)	< 0.001
FBG (mmol/L), median (IQR)	195.0 (160.0–229.0)	192.0 (129.8–241.8)	0.390	0.999 (0.996–1.002)	0.5732
HbA1c (%), median (IQR)	7.4 (6.1–10.0)	9.8 (8.0–15.6)	< 0.001	1.098 (1.048–1.151)	< 0.001
SCR ($\mu\text{mol/L}$), median (IQR)	7.6 (6.8–9.0)	8.0 (6.9–10.2)	0.148	1.122 (0.997–1.262)	0.057
eGFR (ml/min $\times 1.73\text{m}^2$), median (IQR)	71.0 (60.0–86.0)	73.0 (47.8–101.3)	0.677	1.001 (0.998–1.003)	0.506
ALB (g/L), median (IQR)	88.8 (73.8–98.2)	86.8 (63.0–104.3)	0.467	0.993 (0.984–1.003)	0.175
TC (mmol/L), median (IQR)	39.0 (36.5–41)	35.3 (31.8–38.2)	< 0.001	0.861 (0.822–0.902)	< 0.001
TG (mmol/L), median (IQR)	4.2 (3.4–5.1)	4.4 (3.0–5.5)	0.939	0.964 (0.818–1.136)	0.659
HDL (mmol/L), median (IQR)	1.5 (1.2–2.1)	1.4 (1.2–2.2)	0.834	1.010 (0.887–1.150)	0.883
LDL (mmol/L), median (IQR)	1.0 (0.8–1.2)	1.0 (0.7–1.1)	0.243	0.605 (0.240–1.529)	0.228
	2.6 (2.0–3.3)	2.8 (1.7–3.6)	0.889	0.985 (0.787–1.234)	0.898

SAP, stroke-associated pneumonia; OR, odds ratios; SD, standard deviation; IQR, interquartile range; BMI, body mass index, OCSP, Oxfordshire Community Stroke Project; LACI, lacunar circulation infarction; NIHSS, National Institutes of Health Stroke Scale; GNRI, Geriatric Nutritional Risk Index; MI, myocardial infarction; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; NLR, neutrophil-to-lymphocyte ratio; FBG, fast blood glucose; HbA1c, glycosylated hemoglobin; SCR, serum creatinine clearance; eGFR, estimated glomerular filtration rate; ALB, albumin; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

Bold values mean *P*-value < 0.05.

SAP could be obtained by locating the total points on the “Total Points” axis and drawing a vertical line down to the “SAP Risk” axis. For example, the A²DS²-Nutrition

assigns a 50% probability of SAP in a LACI patient (0 points) with A²DS² = 6 (40 points), glucose = 14 mmol/L (45 points), low malnutrition risk (27.5 points), and



hemoglobin = 70 g/L (92.5 points), with a total score of 205 points.

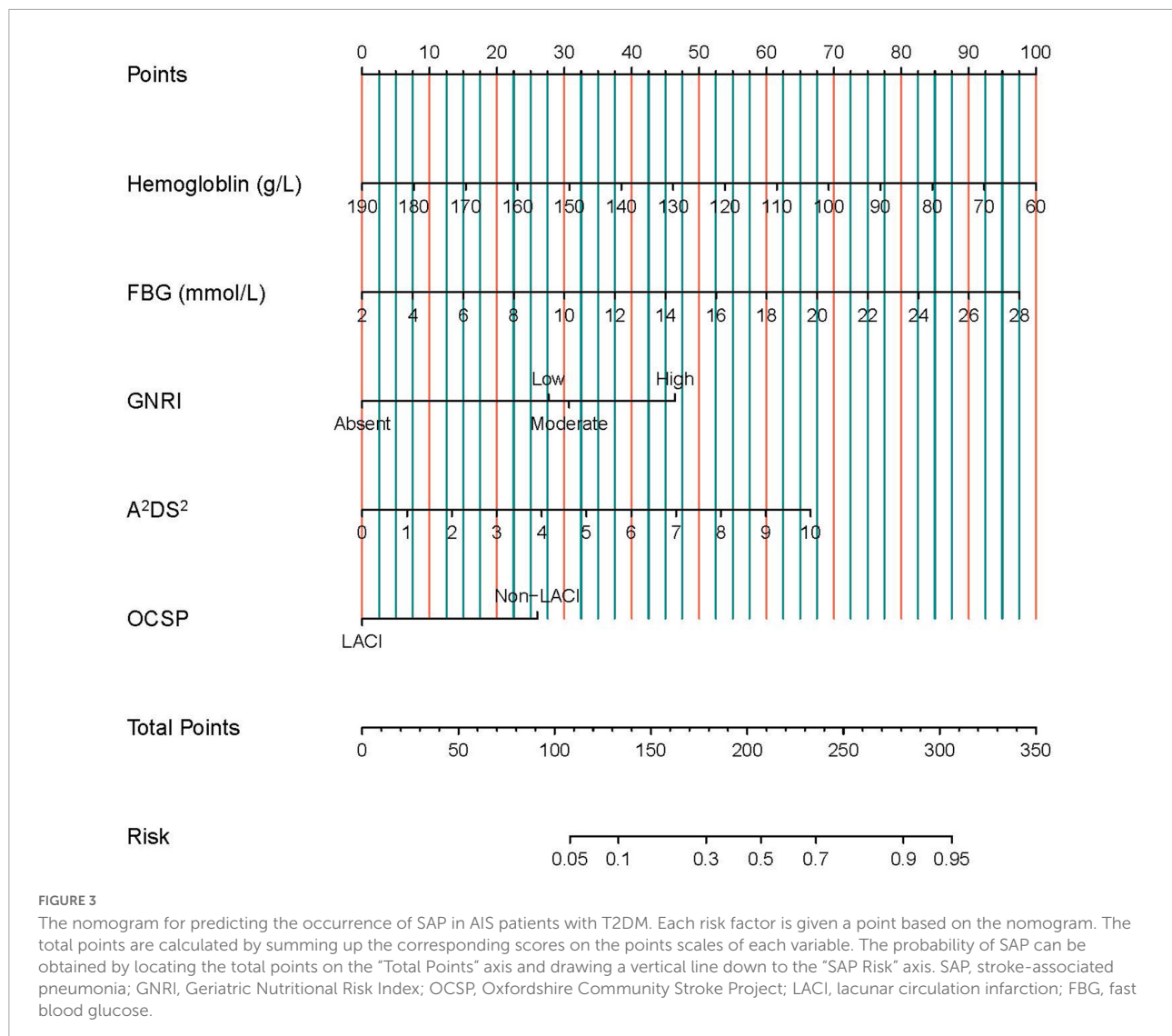
Internal and external validation of the nomogram

The AUROC for this nomogram in the training and validation groups was 0.820 (95% CI: 0.794–0.845) and 0.864 (95% CI: 0.828–0.894), respectively, which were significantly higher than those for A²DS² [trainings group, 0.691 (95% CI: 0.660–0.722); validation group, 0.763 (95% CI: 0.720–0.801)] (Figures 4A,B). In the training group, the calibration plot for SAP probability showed good accordance between the predicted probability and the actual observation (Figure 5A); the mean absolute error was 0.009. Similarly, the calibration plot of the observed against the predicted possibility of SAP demonstrated satisfactory concordance in the validation group; the mean absolute error was 0.015 (Figure 5B). In addition, for a threshold

probability range of 3% to 97%, using the A²DS²-Nutrition would yield a greater net benefit than applying the A²DS² in the training group (Figure 6A). This means that our nomogram is superior to the A²DS² score for treatment decisions (e.g., prophylactic antibiotic therapy) in such a wide range of predefined risk thresholds. For a threshold probability range of 2% to 66%, the A²DS²-Nutrition would provide more net benefit to AIS patients with T2DM than the A²DS² in the validation group (Figure 6B).

Discussion

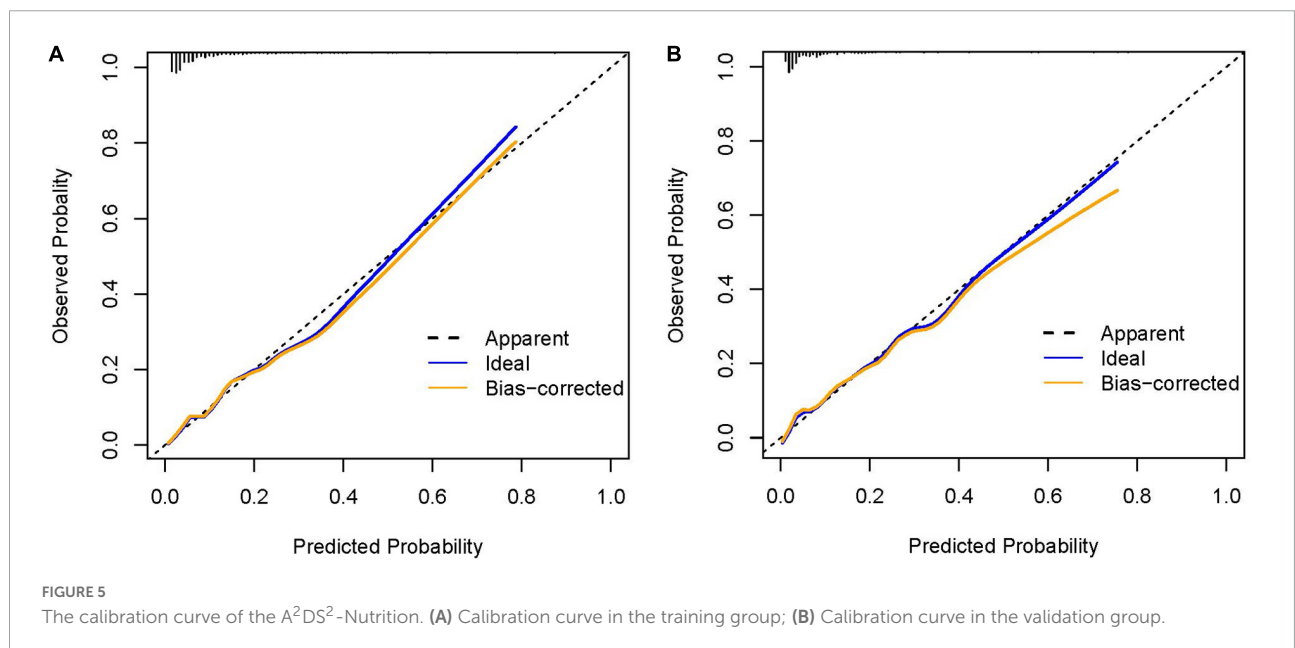
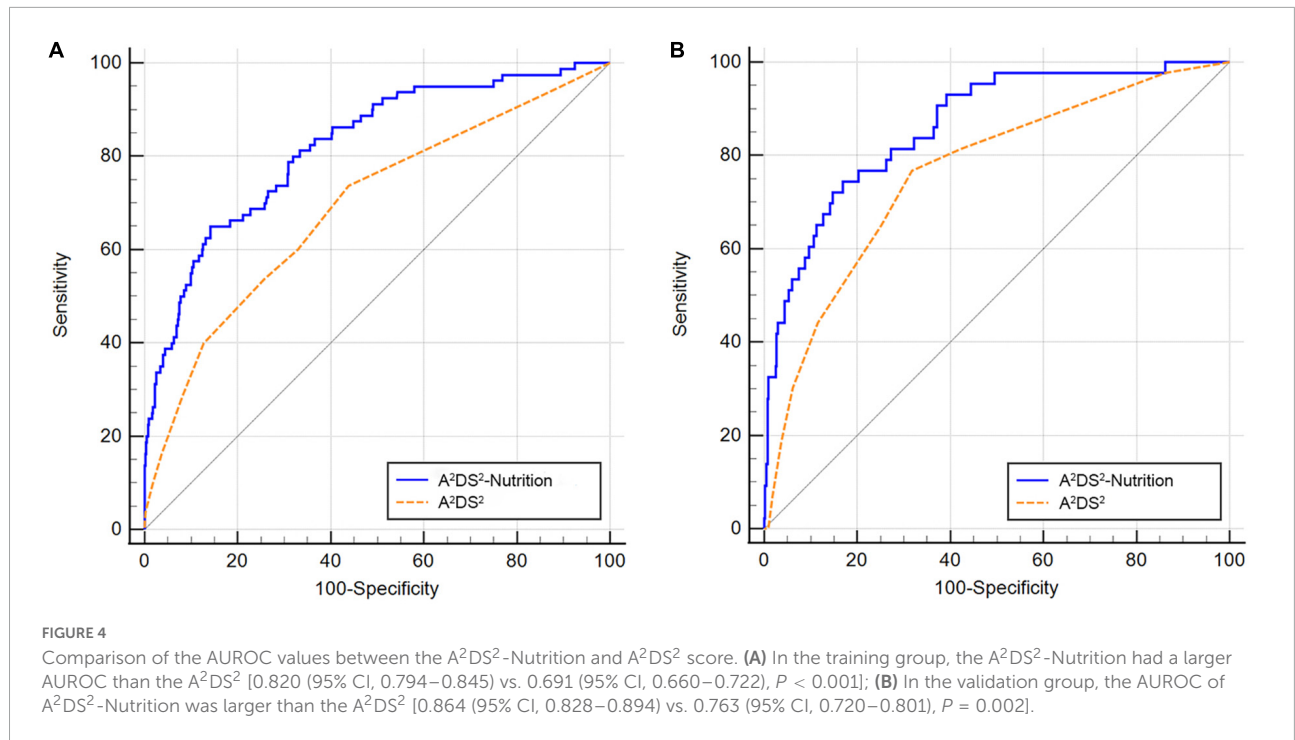
The A²DS² score, stroke classification (non-LACI), GNRI, hemoglobin, and FBG, were independent predictors of SAP in this research. A nomogram was established according to these factors for predicting SAP risk in AIS patients with T2DM. It would assist neurologists in identifying vulnerable patients, making early decisions, and tailoring preventive strategies.



SAP is usually ascribed to stroke-induced immunodepression (5, 6). In addition, pneumonia is more frequent in T2DM patients since hyperglycemia predominantly affects innate immunity (10, 25). Moreover, diabetes is a critical factor for malnutrition in stroke patients [odds ratio (OR) = 2.60, 95% CI: 2.24–3.03] (26), resulting in compromised immunity and increased infection rates (13). Diabetes may increase the risk of pneumonia in people suffering from an ischemic stroke (27, 28). Furthermore, T2DM patients always have poorer clinical outcomes after infection, as evidenced by increased hospitalization incidence, length of stay, and complications (29). Nevertheless, no clinical tool exists to explicitly predict SAP occurrence in AIS patients with T2DM. Although the SAP scoring systems, such as A²DS², have been established for stroke, they have not been specifically validated in the T2DM population. In the present study, the A²DS² score had an insufficient accuracy in predicting SAP

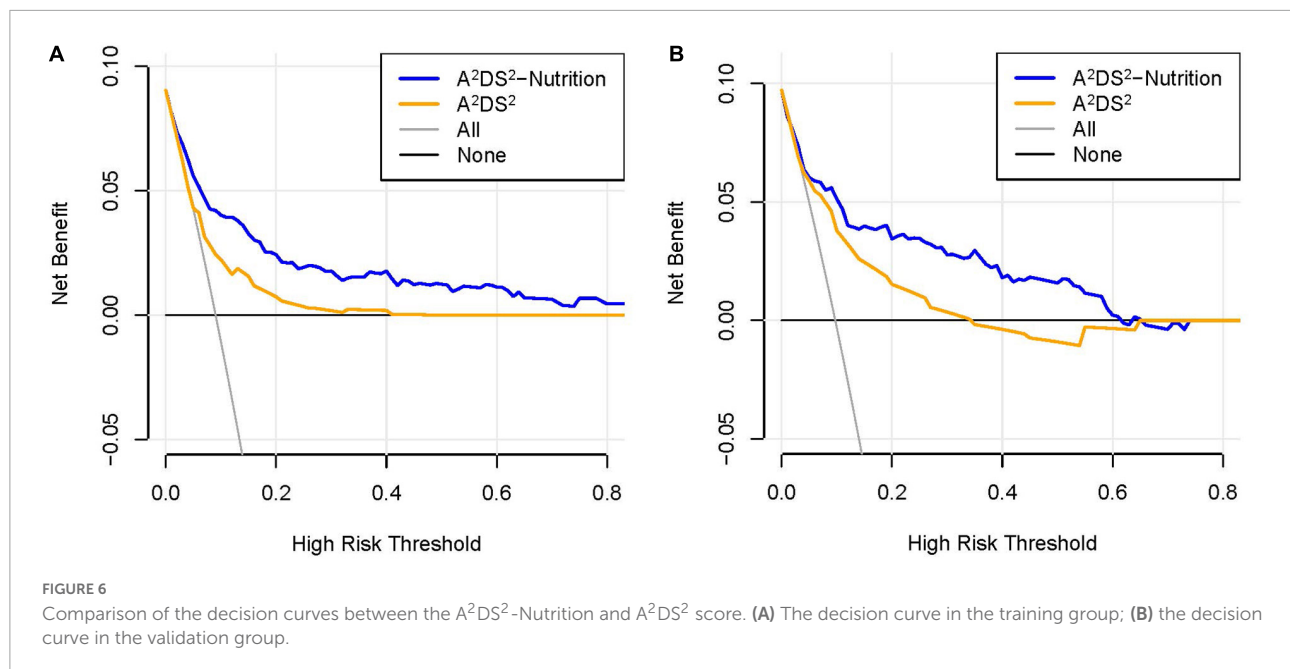
occurrence in the training group [AUROC = 0.691 (95% CI: 0.660–0.722)]. Furthermore, our nomogram had a higher AUROC for discriminating SAP compared with the A²DS² score. This suggests that the A²DS²-Nutrition has a more reliable prediction ability. More importantly, the nomogram assesses the individual risk based on the A²DS² score and nutritional status, which are easily accessible on admission.

The A²DS² score was constructed using data from a large cohort of 15,335 stroke patients in Germany. This research revealed that the score had a high sensitivity (83%) and specificity (72%) (21). The A²DS² score considers age, male sex, atrial fibrillation, dysphagia, and NIHSS, all of which are the mainly elements in other well-recognized SAP scales (30, 31). However, other research reported inconsistencies in A²DS² sensitivities and specificities, probably due to different designs and study populations (15). Therefore, we modified the A²DS² score by in our cohort combining it with stroke



classification and nutritional parameters. The GNRI score is a simple scale system initially designed to assess malnutrition risk among elderly patients (22). Subsequently, the GNRI score was applied to predict sepsis mortality (32) and the probability of surgical site infections (33, 34). Malnutrition risk was found in 5.3% of 8,698 Chinese patients with AIS according to the GNRI score (35). In contrast, 22.1% (294/1330) of our cohort had moderate or severe malnutrition risk defined by GNRI score. A possible reason may be that T2DM patients often

have an improper diet due to poor diabetes-related nutrition knowledge and barriers to dietary adherence (36). In line with this, the malnutrition risk of older COVID-19 patients with diabetes was 2.12 times higher than in those without diabetes in China (37). Lower GNRI scores were associated with an increased risk of long-term death and significant disability in patients with AIS (35). In addition, the GNRI score was employed as a biomarker for SAP risk classification (38). Patients with SAP showed lower GNRI scores than



without SAP (96.88 ± 9.36 vs. 100.88 ± 8.25), indicating its predictive values in AIS patients (38). Considering the high malnutrition risk rate in elderly diabetic patients (11), the GNRI score was included in our prediction model as a critical element.

Hyperglycemia significantly contributed to SAP occurrence in our cohort. This is evidenced by the results of several studies, which demonstrated that glucose level has satisfactory values for predicting SAP (16, 39). Noteworthy, hyperglycemia reduces the neutrophil's bactericidal ability by inhibiting migration, phagocytosis, and superoxide production (40). Furthermore, it may increase the circulation cytokine concentrations, such as tumor necrosis factor- α and interleukin-6, significantly contributing to post-stroke infection (16). In our prediction model, decreased hemoglobin was another independent factor for SAP. Anemia is evaluated to be present in 30% of AIS patients (41). Anemia on admission not only increased the mortality rate (OR = 1.97, 95% CI 1.57–2.47) (41), but also contributed to in-hospital pneumonia incidence (OR = 1.71, 95% CI 1.35–2.17) in stroke patients (42). A reason might be that the anemic patients may be nutritionally imbalanced and immune-compromised. In our study, decreased hemoglobin possibly indirectly reflected the malnutritional risk status of the AIS patients with T2DM.

To our best knowledge, A²DS²-Nutrition is the first nomogram for specifically predicting SAP in AIS patients with T2DM based on routine data. SAP is notorious for increased care dependency, 30-day mortality, and 1-year mortality (5, 6). Hence, our prediction model may facilitate physicians in making individualized decisions, and

implementing early empirical antibiotic therapy, thereby benefiting patients in the long run. Furthermore, the nomogram highlights the need for glycemic control and nutritional support for T2DM patients. A recent study has shown that almost 50% of the patients were non-adherent to their T2DM treatment regimens (43). Thus, hyperglycemia should be strictly monitored and controlled upon admission. Meanwhile, timely nutritional supplements for malnourished individuals may reduce SAP risk.

There remain some limitations in this study. First, to make the nomogram more user-friendly, we did not include infecting-related data (e.g., C-reactive protein and procalcitonin), which were routinely unavailable upon admission in this research. This may affect the accuracy of the prediction model. Second, all the patients were from the same PKUPH center, and the nomogram needs external cohorts to be validated. Finally, our prediction model was developed in the Chinese cohort, limiting the extrapolation of the findings to regions outside our country. However, the model was entirely based on available data, providing the foreign researchers with a new applicable way in the future. Hence, multicenter studies with large sample sizes are required to corroborate the findings of our study.

Conclusion

The A²DS² score, stroke classification, Geriatric Nutritional Risk Index, hemoglobin, and fast blood glucose were independent predictors for SAP in AIS patients with T2DM. The A²DS²-Nutrition might be a simple and reliable tool for predicting SAP occurrence in this population. It may assist

physicians in identifying high-risk patients, making individual decisions, and initiating prophylactic therapies early, thus benefiting the patients in the long run.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee at Peking University People's Hospital. The ethics committee waived the requirement of written informed consent for participation.

Author contributions

JZ and JB designed the study and interpreted the results of this work. YH and XS participated in the data collection. XS and JB analyzed the data and wrote the manuscript. All authors contributed to the discussion and approved the submitted version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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