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Integrating the A^2DS^2 Score with 24-Hour ASPECTS and red cell distribution width for enhanced prediction of stroke-associated pneumonia following intravenous thrombolysis: model development and internal validation

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Abstract

Introduction Stroke-associated pneumonia (SAP) is a major cause of mortality during the acute phase of stroke. The A^2DS^2 score is widely used to predict SAP risk but does not include 24-h non-contrast computed tomography-Alberta Stroke Program Early CT Score (NCCT-ASPECTS) or red cell distribution width (RDW). We aim to evaluate the added prognostic value of incorporating 24-h NCCT-ASPECTS and RDW into the A^2DS^2 score and to develop a novel prediction model for SAP following thrombolysis.

Methods This retrospective cohort study included thrombolyzed AIS patients at Saraburi Hospital, Thailand. The combined A^2DS^2-MFP model incorporated 24-h NCCT-ASPECTS and RDW, along with non-linear continuous predictors, using multivariable fractional polynomial (MFP) regression. Predictive performance was evaluated using the area under the receiver operating characteristic curve (AuROC), calibration plots, and decision curve analysis (DCA), comparing it with the traditional A^2DS^2 model and a model with continuous predictors. The goodness of fit for logistic regression models in relation to the observed data was determined through the Hosmer–Lemeshow method, and the accuracy of the probability predictions was examined using a calibration curve. Internal validation was performed using a bootstrapping approach. The predicted probability equation obtained from the final model after optimism correction was developed into a web-based application for predicting the risk of SAP, using PHP and JavaScript.

Results Of 345 AIS patients, 20.3% developed SAP. The combined A^2DS^2-MFP model demonstrated excellent discriminative performance (AuROC: 0.917) compared to the traditional A^2DS^2 model (AuROC: 0.868) and the model with continuous predictors (AuROC: 0.888). Both the calibration curve and the Hosmer–Lemeshow test indicated that the predicted probabilities and observed frequencies were in acceptable agreement. Incorporating 24-h NCCT-ASPECTS and RDW significantly improved risk prediction and clinical utility, as shown by improved reclassification indices and DCA. The model was internally validated with a C-statistic of 0.912, confirming its robustness.

Conclusions The combined A^2DS^2-MFP calculation showed superior performance, enabling early SAP detection and improving survival outcomes. This novel model offers a practical tool for resource-limited settings, supporting better SAP risk stratification and clinical management.

Keywords ASPECTS, A^2DS^2 score, Ischemic stroke, Stroke-associated pneumonia, Thrombolysis

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Introduction

Ischemic stroke and its complications contribute to global mortality and functional impairment [1]. Endovascular thrombectomy (EVT) advances acute ischemic stroke (AIS) treatment, but its availability is limited. Thrombolytic treatment is effective for AIS within a 4.5-h window [2]. Stroke-associated pneumonia (SAP), occurring mostly in the first three days, impacts clinical outcomes with an incidence of 11–14% [3]. SAP is a preventable condition that contributes to higher mortality rates, hospital stays, and recovery challenges. Early diagnosis and targeted care are vital for better outcomes [4]. Established models for early SAP detection include the A^2DS^2 scale (Age, Atrial fibrillation [AF], Dysphagia, Sex, Stroke Severity) [5], ISAN scale [6], and AIS-APS scale [7], with the A^2DS^2 score demonstrating superior predictive performance [8]. However, these models are based solely on clinical data. Therefore, exploring the added prognostic value of incorporating neuroimaging findings and inflammatory biomarkers, which are routinely available in clinical settings, remains an area with limited data and warrants further investigation.

Non-contrast CT (NCCT) and diffusion-weighted imaging play a critical role in identifying early ischemic changes (EICs) and evaluating the efficacy of thrombolytic treatments. [9, 10]. The Alberta Stroke Program Early CT Score (ASPECTS) assesses EICs, predicts functional outcomes, and aids in EVT patient selection. In resource-limited settings like Thailand, 24-h NCCT-ASPECTS serves as a valuable predictor of SAP events after thrombolysis and may help identify high-risk patients for timely intervention [11].

The red cell distribution width (RDW), a measure of variability in the size of red blood cells (RBC), is represented as the coefficient of variation in erythrocyte size [12]. RDW shows a relationship with inflammation markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), which are valuable indicators of inflammation and the intensity of the inflammatory response [13, 14]. Elevated immune responses may produce cytokines that worsen lung inflammation, increasing severe complications and secondary infection risks [15]. Stroke further triggers an inflammatory cascade and stroke-induced immunodepression syndrome (SIDS), impairing immune defenses against pathogens and heightening the risk of secondary infections, including SAP [16]. As a routine component of the CBC and more cost-effective than CRP or ESR, RDW offers a practical and accessible predictor for SAP, particularly in resource-limited settings. RDW reflects the inflammatory state associated with stroke-related brain injury and complications, providing prognostic value.

The A^2DS^2 score does not include 24-h NCCT-ASPECTS or RDW, and incorporating these variables may enhance its predictive accuracy. This study aims to evaluate the prognostic value of combining 24-h NCCT-ASPECTS and RDW with the A^2DS^2 score and to develop a novel model for predicting SAP after thrombolysis.

Methods

Study population

This retrospective observational study included 345 consecutive AIS patients who received thrombolytic therapy at the Stroke Unit of Saraburi Hospital, a tertiary care center in central Thailand, between January 2015 and July 2022. The study represents a secondary analysis of data from previous research [11]. None of the AIS patients in this study were intubated or had significant organ failure, as those with such conditions were admitted to the intensive care unit. During the Coronavirus Disease 2019 (COVID-19) pandemic, SAP cases excluded COVID-19 infections, as patients with evidence of COVID-19 infection were managed separately in designated COVID wards.

Inclusion and exclusion criteria

At our clinical centers, all patients included in the study were clinically diagnosed with AIS based on World Health Organization criteria and received thrombolytic therapy within 3 to 4.5 h of symptom onset, in accordance with the 2019 guidelines for the early management of AIS [17]. The exclusion criteria were as follows: (1) a history of infection or antibiotic use within the previous two weeks, (2) incomplete medical records, (3) a history of dysphagia prior to the stroke (as it can lead to aspiration pneumonia and confound the risk of SAP), (4) discharge or death within 72 h of symptom onset, (5) severe hepatic diseases (as these are related to systemic inflammation and can confound RDW levels), (6) treatment with EVT, (7) thrombolysis-related intracerebral hemorrhage (ICH) within 24 h, and (8) transfer to another hospital where follow-up treatment data were unavailable. Our center encountered significant obstacles in performing EVT during the study. Limited EVT access, due to public health reimbursement policies, restricted referrals for eligible cases during the study period. Systemic thrombolysis with alteplase at the standard dose of 0.9 mg/kg was administered to all patients, with informed consent provided by the patients or their families.

Ethical approval

Ethics approval (EC 043/2566) was granted by the hospital's Institutional Review Board, with consent waived for retrospective data analysis. Study procedures are

available on the Open Science Framework at https://osf.io/mru7h.

Data collection

Key clinical variables included demographic data (age, gender), medical history (AF, dysphagia), and stroke severity, measured using the baseline National Institutes of Health Stroke Scale (NIHSS). Laboratory evaluations included CBC analysis performed with the Sysmex XN-3000 automated analyzer. We gathered and evaluated radiological factors, focusing primarily on the 24-h NCCT-ASPECTS (assessed 24 h after thrombolytic treatment) using a 160-slice TOSHIBA Aquilion Prime CT scanner with 3 mm axial slices.

Measurements

To minimize misclassification bias, the ASPECTS score was evaluated by two independent authors—a neurologist (SK) and a neuroradiologist (NA)—blinded to the clinical data, with discrepancies resolved by consensus. Dysphagia was evaluated within 24 h using the Modified Water Swallowing Test [18], consisting of three trials rated on a 5-point scale. A score below 4, determined by a rehabilitation physician, indicated the presence of dysphagia.

Outcomes

SAP was defined as pulmonary infections within 7 days of stroke onset in non-ventilated patients and was diagnosed using modified Centers for Disease Control and Prevention guidelines [19] and/or Mann's criteria [20]. Patients meeting definite or probable SAP criteria under either guideline were classified as having SAP.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation, and categorical variables as frequency and percentage. Fisher's exact test was used to compare categorical variables, while the independent t-test and Wilcoxon rank-sum test were used to assess continuous variables with normal and skewed distributions, respectively. Predictive ability was evaluated using the area under the receiver operating characteristic (AuROC) curve. All analyses were based on a complete-case analysis approach, as the proportion of missingness was small (5.5%); therefore, this approach is unlikely to bias the results [21–23]. Statistical analyses were performed in Stata 16 (StataCorp, College Station, TX, USA) with significance set at $P < 0.05$.

Model development and assessing the added value of prognostic analysis

Three logistic regression models were developed to predict SAP in thrombolyzed AIS patients. Model A, based on the traditional A^2DS^2 score, dichotomized continuous variables and included the following components: age ≥ 75 years (1 point), male sex (1 point), AF (1 point), dysphagia (2 points), NIHSS 5–15 (3 points), and NIHSS ≥ 16 (5 points). Model B (A^2DS^2-c) incorporated continuous variables as linear terms and applied multivariable logistic regression (MVLR) using age and NIHSS as continuous variables, and AF, dysphagia, and male sex as binary variables. Model C (combined A^2DS^2-MFP calculation) integrates the A^2DS^2 score, 24-h NCCT-ASPECTS, and RDW using multivariable fractional polynomial (MFP) regression to optimize the binary logistic model [24]. Continuous variables (age, NIHSS, 24-h NCCT-ASPECTS, and RDW) were modeled as non-linear functions for improved precision, while AF, dysphagia, and male sex were included as binary factors.

Model performance was assessed by discrimination (AuROC) and calibration (calibration plot). Goodness-of-fit of the model was examined using Hosmer–Lemeshow test. Added predictive value was determined using AuROC, integrated discrimination improvement (IDI), and category-based net reclassification index (cb-NRI, 50% probability cutoff). Logistic regression equations were the basis for each prediction model, with SAP probability derived by transforming the linear predictor (lp) through an inverse logit function using the formula $e^{lp}/(1+e^{lp})$, where 'e' is the natural logarithm base. We visually assessed the model's calibration using a calibration plot, which compares observed and predicted probabilities for SAP after dividing the observed risk into deciles [25]. Additionally, a calibration intercept (calibration-in-the-large, CITL) of zero indicates no systematic overestimation or underestimation of predicted probabilities, while a calibration slope (C-slope) of one suggests perfect agreement between observed and predicted probabilities.

Model internal validation and clinical utility

Internal validation of the combined A^2DS^2-MFP calculation (Model C) was performed using bootstrapping with 500 samples, assessing performance metrics (AuROC, calibration slope, calibration-in-the-large). Optimism adjustments were applied to model's intercept and coefficients (slope). Decision curve analysis (DCA) evaluated clinical utility across models, examining net benefit (NB) for high-risk SAP patients [26].

A web-based tool for SAP risk prediction was developed using the combined A^2DS^2-MFP calculation to support personalized management. Patients with positive

likelihood ratios (LR+) ≥ 10 (indicating a predicted risk of approximately ≥ 50%) should receive early intervention, while those with LR+ between 1 and 10 require individualized assessment.

Study size considerations

With seven candidate predictors (age, gender, AF, dysphagia, NIHSS, 24-h NCCT-ASPECTS, RDW), a minimum of 70 SAP cases was required, ensuring at least 10 events per variable (EPV) as recommended TRIPOD guidelines [27] and previous literature [28].

Results

Baseline characteristics

A total of 400 AIS patients treated with thrombolytic therapy were initially enrolled in the study. Of these, 55 were excluded for the following reasons: recent active infection (n = 5), incomplete medical records (n = 22), referral to another hospital (n = 6), death within three days (n = 10), and thrombolysis-related ICH within 24 h (n = 12). The final analysis included 345 participants.

Among the 345 AIS patients treated with thrombolysis, 70 (20.3%) developed SAP. Significant differences in age (68.10 ± 14.28 vs. 60.17 ± 15.07, $P < 0.001$), AF (50.0% vs. 24.4%, $P < 0.001$), dysphagia (88.6% vs. 24.4%, $P < 0.001$), NIHSS score (17.56 ± 4.85 vs. 11.22 ± 5.11, $P < 0.001$), and A^2DS^2 score (7.61 ± 1.56 vs. 4.76 ± 1.81, $P < 0.001$) were observed between groups. Furthermore, neuroimaging and laboratory results differed significantly, with lower 24-h NCCT-ASPECTS (3.90 ± 2.70 vs. 7.75 ± 2.57, $P < 0.001$) and higher RDW values (15.70 ± 2.94 vs. 14.51 ± 1.91, $P < 0.001$) in SAP patients (Table 1). Notably, compared to various CBC parameters, RDW showed the best discrimination for SAP (AuROC = 0.621, 95% CI 0.541, 0.701) (S1 Table).

Risk discrimination, reclassification, and added value by incorporating 24-h ASPECTS and RDW

The prognostic impact of 24-h ASPECTS and RDW on the A^2DS^2 score is shown in Tables 2 and 3. The traditional A^2DS^2 score, A^2DS^2-c calculation, and combined A^2DS^2-MFP calculation demonstrated AuROC values of 0.868 (95% CI 0.823, 0.914), 0.888 (95% CI 0.847, 0.929), and 0.917 (95% CI 0.881, 0.952), respectively (Table 2 and Fig. 1). Pairwise comparisons revealed that the combined A^2DS^2-MFP calculation (Model C) significantly

Table 1 Clinical characteristics of patients and A^2DS^2 score results

Characteristics	All patients (n = 345)	SAP (n = 70)	Non-SAP (n = 275)	*P*-value
Age (years)	61.78 ± 15.23	68.10 ± 14.28	60.17 ± 15.07	< 0.001
Gender				
Male	53 (53.0)	38 (54.3)	145 (52.7)	0.816
Female	47 (47.0)	32 (45.7)	130 (47.3)	
Atrial fibrillation	30 (29.6)	35 (50.0)	67 (24.4)	< 0.001
Dysphagia	37 (37.4)	62 (88.6)	67 (24.4)	< 0.001
NIHSS at admission				
5–15	67 (67.3)	17 (24.3)	215 (78.2)	< 0.001
≥ 16	33 (32.8)	53 (75.7)	60 (21.8)	
Baseline NIHSS	12.51 ± 5.66	17.56 ± 4.85	11.22 ± 5.11	< 0.001
Laboratory and ASPECTS				
WBC ($\times 10^3$/μL)—mean (SD)	8.96 ± 3.16	10.23 ± 4.88	8.64 ± 2.45	< 0.001
ANC ($\times 10^3$ cell/mm^3)—mean (SD)	5.82 ± 3.16	7.08 ± 5.14	5.49 ± 2.31	< 0.001
ALC ($\times 10^3$ cell/mm^3)—mean (SD)	2.41 ± 1.11	2.39 ± 1.25	2.42 ± 1.08	0.867
NLR—Median (IQR)	2.21 (1.50, 3.70)	2.69 (1.61, 5.27)	2.17 (1.46, 3.57)	0.052
PNR—mean (SD)	50.68 ± 25.83	46.45 ± 25.38	51.75 ± 25.88	0.126
PLR—median (IQR)	107.16 (79.37,147.92)	105.95 (75.04, 149.54)	107.49 (80.18, 147.92)	0.861
RDW (%)– mean (SD)	14.75 ± 2.21	15.70 ± 2.94	14.51 ± 1.91	< 0.001
RPR—mean (SD)	6.48 ± 2.59	7.02 ± 3.58	6.34 ± 2.25	0.051
24-h ASPECTS				
Mean ± SD	6.97 ± 3.02	3.90 ± 2.70	7.75 ± 2.57	< 0.001
Median (IQR)	8 (5, 9)	4 (2, 6)	9 (7, 10)	< 0.001
A^2DS^2 score	5.34 ± 2.10	7.61 ± 1.56	4.76 ± 1.81	< 0.001

ASPECTS, Alberta Stroke Program Early CT Score; A^2DS^2, (Age, Atrial fibrillation, Dysphagia, Sex, Stroke Severity); ANC, absolute neutrophil count; ALC, absolute lymphocyte count; NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil-to-lymphocyte count ratio; PLR, platelet-lymphocyte ratio; PNR, platelet-to-neutrophil ratio; RDW, red cell distribution width; RPR, red cell distribution width to platelet ratio; SAP, stroke associated pneumonia; WBC, white blood cell

Table 2 Evaluation of the prognostic value of 24-h ASPECTS and RDW to the A^2DS^2 score for predicting SAP with MFP transformation of continuous parameters

Models	Cut-off values/optimal FP transformation	β	(95%CI)	*P*-value	AuROC	(95% CI)
*Model A: Traditional A^2DS^2 score					0.868	(0.823, 0.914)
†Model B: A^2DS^2-c calculation					0.888	(0.847, 0.929)
Age	Original continuous form	0.025	(0.001, 0.050)	0.046		
NIHSS	Original continuous form	0.109	(0.038, 0.179)	0.003		
AF	Original binary form	0.756	(0.069, 1.444)	0.031		
Dysphagia	Original binary form	2.510	(1.642, 3.378)	< 0.001		
Male	Original binary form	0.178	(– 0.510, 0.866)	0.613		
Intercept (constant)	–	– 6.437	(– 8.511, – 4.364)	< 0.001		
Added predictive factor						
24-h ASPECTS	Original continuous form	– 0.419	(– 0.519, – 0.319)	< 0.001	0.841	(0.789, 0.893)
RDW	Original continuous form	0.209	(0.099, 0.319)	< 0.001	0.621	(0.541, 0.701)
‡Model C: Combined A^2DS^2-MFP calculation					0.917	(0.881, 0.952)
Age	Age-61.777	0.039	(0.011, 0.067)	0.006		
NIHSS	NIHSS-12.507	0.027	(– 0.060, 0.115)	0.542		
AF	Original binary form	0.432	(– 0.318, 1.182)	0.259		
Dysphagia	Original binary form	2.291	(1.354, 3.229)	< 0.001		
Male	Original binary form	0.281	(– 0.458, 1.019)	0.456		
24-h ASPECTS	$([24\text{-h ASPECTS} + 1]/10)^3$–0.506	– 2.177	(– 3.306, – 1.048)	< 0.001		
RDW	RDW-14.750	0.218	(0.063, 0.373)	0.006		
Intercept (constant)	–	– 3.339	(– 4.293, – 2.384)	< 0.001		

A^2DS^2 score, (Age, Atrial fibrillation, Dysphagia, Sex, Stroke Severity); *AF* atrial fibrillation; *ASPECTS* Alberta Stroke Program Early CT Score; *AuROC* area under the receiver operating characteristic curve; *CI* confidence interval; *FP* fractional polynomial; *MFP* multivariable fractional polynomial; *NIHSS*, National Institutes of Health Stroke Scale; *RDW* red blood cell distribution width; *SAP* stroke associated pneumonia

* Model A includes traditional A^2DS^2 score; † Model B includes A^2DS^2-c calculation; ‡ Model C includes combined A^2DS^2-MFP calculation)

§ Model B: predicted risk (equation): $e^{lp}/(1+e^{lp})$, where lp = – 6.437 + 0.025 (Age) + 0.109 (NIHSS) + 0.756 (AF) + 2.510 (Dysphagia) + 0.178 (Male); Model C: Predicted risk (equation): $e^{lp}/(1+e^{lp})$, where lp = – 3.339 + 0.039 (Age-61.777) + 0.027 (NIHSS-12.507) + 0.432 (AF) + 2.291 (Dysphagia) + 0.281 (Male) + – 2.177 ([(24-h ASPECTS + 1)/10]^3–0.506) + 0.218 (RDW-14.750)

Table 3 Improvement in model performance by combined A^2DS^2-MFP calculation in prediction of SAP

Metrics	Model A* vs. Model B†		Model A* vs. Model C‡		Model B† vs. Model C‡	
	Value	*P*-value	Value	*P*-value	Value	*P*-value
Δ AuROC	0.020 (– 0.001, 0.038)	0.055	0.049 (0.014, 0.081)	0.005	0.029 (0.004, 0.053)	0.021
IDI						
Absolute	0.044 (0.016, 0.072)	0.002	0.126 (0.080, 0.172)	< 0.001	0.086 (0.044, 0.127)	< 0.001
Relative	1.123		1.378		1.230	
NRI						
Overall	0.078 (0.008, 0.148)	0.028	0.222 (0.104, 0.339)	< 0.001	0.118 (0.014, 0.222)	0.025
Events correctly reclassified	8.6%		21.4%		10.0%	
Nonevents correctly reclassified	– 0.7%		0.7%		1.8%	

AuROC area under the receiver operating characteristic curve; *IDI* integrated discrimination improvement; *NRI* Net reclassification index; *MFP* multivariable fractional polynomial; *SAP* stroke associated pneumonia

* Model A includes traditional A^2DS^2 score; † Model B includes A^2DS^2-c calculation; ‡ Model C includes combined A^2DS^2-MFP calculation

improved SAP prediction, with Δ AuROC of 0.049 (95% CI 0.014, 0.081; $P=0.005$) compared to the traditional A^2DS^2 (Model A) score and 0.029 (95% CI 0.004, 0.053; $P=0.021$) compared to the A^2DS^2-c calculation (Model B). Model C also showed higher IDI: 0.126 (95% CI 0.080, 0.172; $P<0.001$) and 0.086 (95% CI 0.044, 0.127; $P<0.001$), as well as higher NRI: 0.222 (95% CI 0.104, 0.339; $P<0.001$) and 0.118 (95% CI 0.014, 0.222;

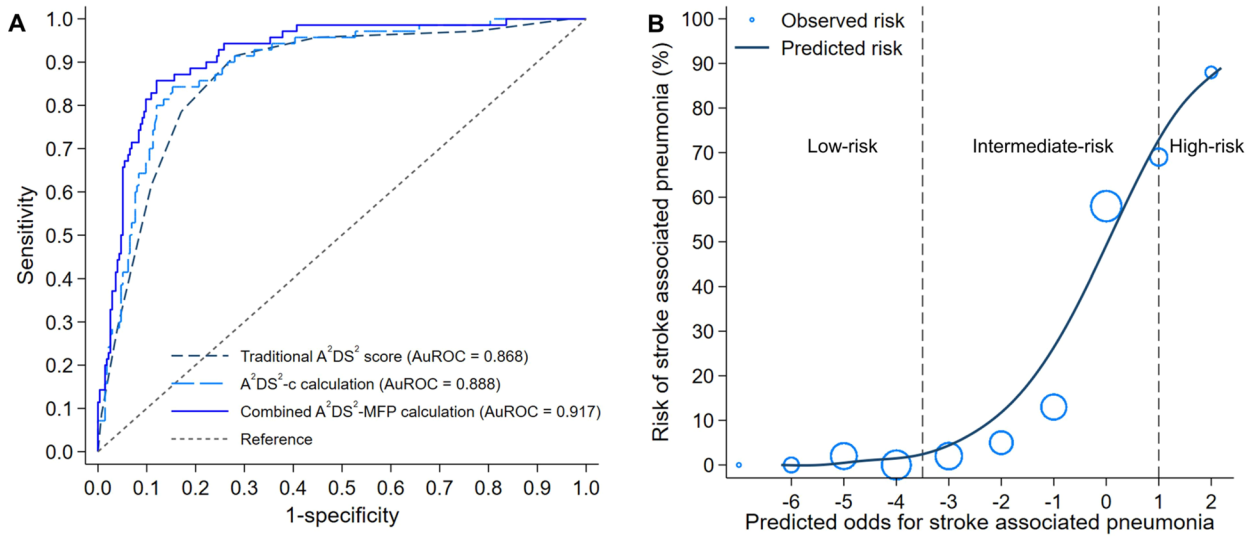

Fig. 1 **A** ROC curve for the clinical prediction model with the combined A^2DS^2-MFP calculation (A^2DS^2 score with 24-h ASPECTS and RDW) in thrombolyzed AIS patients; **B** Calibration plot showing the agreement between predicted odds and observed risk of SAP for each decile of predicted odds

$P<0.001$), compared to models A and B, respectively, indicating better risk discrimination and reclassification.

Model internal validation and clinical utility

The combined A^2DS^2-MFP calculation showed excellent discriminative performance with an AuROC of 0.917 (95% CI 0.881, 0.952) (Fig. 1a). The calibration plot (Fig. 1b) demonstrated good alignment between predicted risk and actual SAP proportions in each decile. Figures 2A–C visualize the agreement between predicted SAP probabilities and observed SAP proportions for all three models. A non-significant Hosmer–Lemeshow goodness-of-fit result ($P=0.526$) for the A^2DS^2-MFP model suggests that the model fits the data well by comparing observed and expected events within probability-defined groups. Internal validation using the bootstrap approach revealed an optimism-adjusted model with a C-statistic of 0.912, a calibration in the large of − 0.014, and a calibration slope of 0.895 (S2 Table). Beta coefficients and intercept values for both the original and optimism-adjusted models are provided in S3 Table. Calibration of the internal validation using bootstrap resamples and optimism correction is shown in Figs. 2D and 2E.

Model prognostic accuracy

The combined A^2DS^2-MFP calculation exhibits superior discriminative capabilities compared to the traditional A^2DS^2 score and A^2DS^2-c calculation. The calculation of SAP-predicted probabilities from the final model after optimism correction follows this equation: Probability = $e^{lp}/(1+e^{lp})$, where lp = (− 3.339 + 0.014) + 0.895*(0.039*(Age-61.777) + 0.027*(NIHSS-12.507) + AF*0.432 + Dysphagia*2.291 + Male*0.281 — 2.177*(((24-h ASPECT + 1)/10)^3–0.506) + 0.218*(RDW-14.750)). For clinical use, we categorized predicted probabilities into three risk groups: low-risk (< 5.0%), intermediate-risk (5.0–49.9%), and high-risk (≥ 50%). The PPV and LR + pertaining to each risk category are depicted in S4 Table.

The decision curve analysis showed that the combined A^2DS^2-MFP calculation offers a higher NB than default strategies (treating all or no patients as SAP) across threshold probabilities (Fig. 3). Compared to the traditional A^2DS^2 score and A^2DS^2-c calculation, the combined A^2DS^2-MFP calculation outperforms at various predicted risk thresholds (10%–50%), with better sensitivity, specificity, PPV, negative predictive value, LR +, and overall accuracy (S5 Table).

To facilitate clinical use, the prediction tool is available online at https://www.sbh.go.th/sap/ (accessed September 12, 2023). Screenshots of the tool's web interface are presented in S1 Fig. For demonstration, we applied the tool to a case involving an 87-year-old male with a history of AF and hypertension. He presented to the hospital with right-sided hemiparesis and aphasia. His initial NIHSS score was 18, and his baseline NCCT-ASPECTS was 7. The patient received thrombolytic treatment, and 24 h after thrombolysis, a repeat NCCT showed a 24-h NCCT-ASPECTS score of 4. Swallowing

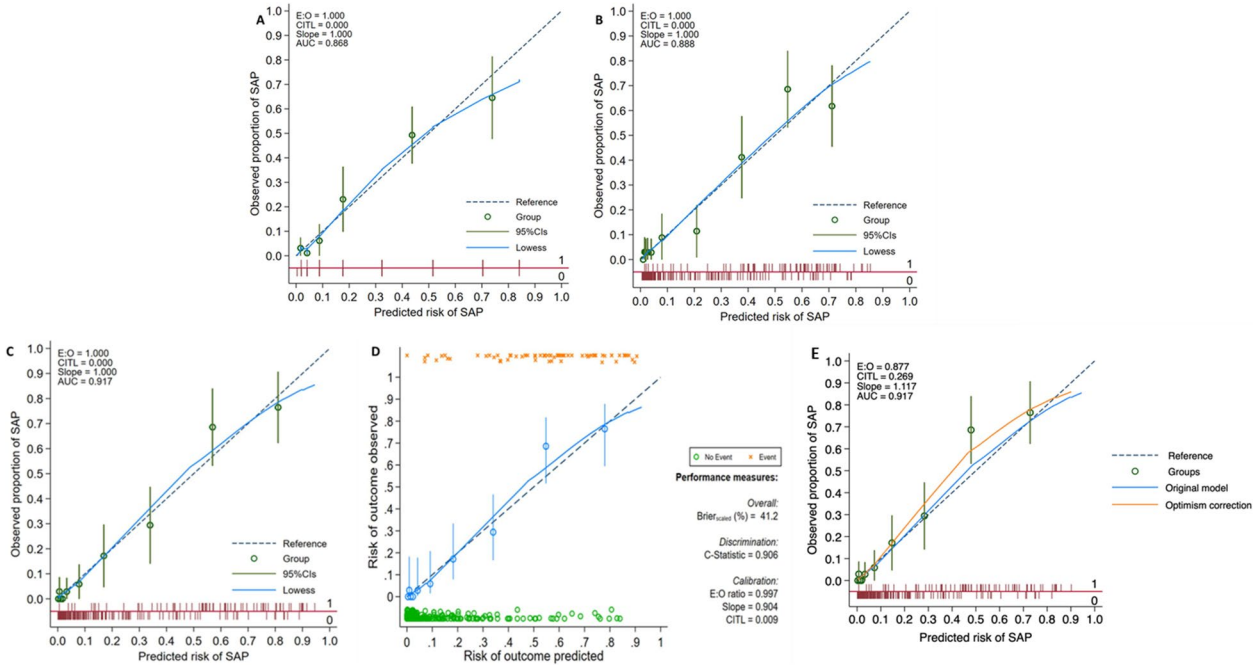

Fig. 2 Calibration plots comparing the predicted risk of SAP in thrombolyzed AIS patients: **A** Traditional A^2DS^2 score, **B** A^2DS^2-c calculation, **C** Combined A^2DS^2-MFP calculation, **D** Internal validation of the combined A^2DS^2-MFP calculation using 500 bootstrap resamples, and **E** Comparison of calibration plots between the original and optimism-corrected combined A^2DS^2-MFP model. *Note:* The 45-degree line represents ideal agreement between observed and predicted probabilities. Vertical bars indicate the 95% CI of the actual probability

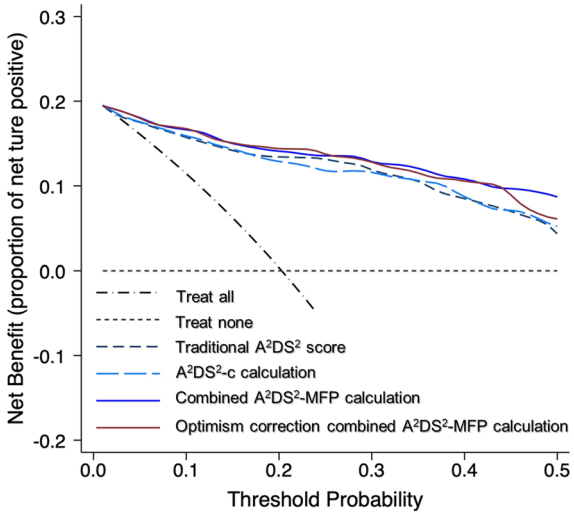

Fig. 3 Decision curve analysis showing the net benefit of the combined A^2DS^2-MFP calculation

tests revealed dysphagia, and his RDW was 15.5%. Using the web-based application, we input the patient's data, the calculated SAP probability for this patient was 85.7%, classifying him as high risk (S2 Fig).

Discussion

This study developed and internally validated a novel prediction model integrating the A^2DS^2 score, 24-h NCCT-ASPECTS, and RDW using MVLR and MFP techniques. Among 345 AIS patients, 20.3% developed SAP. The A^2DS^2-MFP model demonstrated superior predictive performance (AuROC: 0.917) compared to traditional models, highlighting its potential to improve SAP risk stratification in thrombolyzed AIS patients.

When comparing the incidence of SAP in this study to previous research, notable differences emerge. Prior studies reported SAP incidence rates ranging from 9 to 14% [8, 29], whereas our study observed a higher incidence of 20.3%. This disparity likely stems from our broader inclusion criteria, encompassing both probable and definite SAP cases to enhance detection sensitivity. In contrast, earlier studies relied on more restrictive diagnostic definitions. In fact, if we had limited our analysis to definite SAP cases only, the incidence would have dropped to 13.2%. Additionally, variations in observation durations, clinician thresholds for initiating antibiotics, and patient characteristics may also contribute to these differences. These findings highlight the need for standardized diagnostic criteria in future studies to enable more consistent comparisons.

In previous studies, 24-h NCCT-ASPECTS was a robust predictor of SAP (OR: 5.33, 95% CI 2.08–13.67, $P < 0.001$). A score of ≤ 6 had higher sensitivity (0.84 [95% CI 0.74–0.92]) and specificity (0.79 [95% CI 0.74–0.84]) compared to baseline and change in ASPECTS. It also demonstrated superior predictive performance for SAP, with an AuROC of 0.84, versus 0.75 and 0.82 for baseline and change in ASPECTS, respectively [11]. Stroke-induced immunodepression syndrome (SIDS) may explain the link between a decreased NCCT-ASPECTS score and a higher risk of SAP. Specifically, extensive infarction, as indicated by a lower ASPECTS score, can impair immune function by causing lymphocytopenia, deactivation of T helper cells, and monocyte dysfunction [30, 31]. Additionally, brain infarction can activate the sympathetic nervous system, triggering the release of catecholamines, which reduce circulating lymphocytes and weaken the antibacterial immune response following AIS [32]. These combined changes weaken the body's defense against pathogens, thereby increasing the risk of infection, including SAP.

Previous studies derived that RDW is associated with stroke severity and unfavorable functional outcomes at 3 months in AIS patients [33], but its relationship with SAP is still unclear. In this study, RDW was one of the potential independent predictors of SAP. Elevated RDW levels might indicate a condition in which RBC production and turnover slow down, while white blood cell and platelet production increases during inflammation. Persistent inflammation and reduced antioxidants lead to oxidative stress, which can impact secondary infections [34]. RDW may reflect a broader perspective on the underlying inflammatory state and oxidative stress damage, impacting brain injury and early post-stroke infection, and emerging as a novel predictor with promising prognostic value [35]. Admission RDW may better identify early inflammatory responses than other CBC parameters, which are specific to acute inflammation and peak 12–72 h after stroke onset [36]. Previous research suggested that male gender significantly predicted SAP susceptibility, even after considering potential confounding factors. This increased risk in males was linked to their higher rates of smoking and pre-existing pulmonary conditions [37, 38]. In contrast, our study found no association between sex differences and SAP.

Previous research showed that the A^2DS^2 score was effective for predicting SAP and assessing stroke prognosis in AIS patients [5, 39]. However, neuroimaging data and laboratory parameters are crucial for enhancing the predictive performance. In this study, we integrated 24-h NCCT-ASPECTS and RDW with the A^2DS^2 score to create a more straightforward and practical approach. The combined A^2DS^2-MFP calculation improved the AuROC to 0.917, providing superior predictive performance over the traditional A^2DS^2 and A^2DS^2-c calculation. It enables more accurate identification, better risk stratification, and enhanced clinical utility for patients at risk of SAP. Healthcare providers can prioritize interventions for high-risk patients and allocate resources more effectively, potentially reducing complications and improving stroke outcomes [40]. Designed as a web-based tool, it provides seamless access via desktop and mobile devices, allowing clinicians to input patient data, generate real-time SAP risk estimates, and categorize patients into low-, intermediate-, and high-risk groups. High-risk patients may benefit from early prophylactic antibiotic therapy, aspiration precautions, and dysphagia rehabilitation, while intermediate-risk patients may require closer monitoring and preventive interventions. Low-risk patients can follow standard care protocols, optimizing resource allocation and improving clinical workflows.

From a research perspective, this study emphasizes the importance of integrating neuroimaging and laboratory biomarkers into traditional clinical scores to enhance predictive accuracy. It also raises a cautionary note regarding the oversimplification of continuous predictors through dichotomization, which may compromise a model's ability to identify risk accurately. Future studies should evaluate the model's performance in EVT-treated populations and explore additional biomarkers to refine SAP risk prediction further.

This study has several strengths. First, it represents the first attempt to integrate the A^2DS^2 score with 24-h NCCT-ASPECTS and RDW, resulting in a highly accurate prediction model. Second, the incorporation of readily available and cost-effective parameters enhances the model's clinical applicability, especially in resource-limited settings. Third, the retention of continuous variables through the non-linear MFP method preserves data granularity and improves predictive accuracy compared to previous studies, where all continuous predictors were dichotomized before modeling [5–7]. Fourth, the 24-h NCCT-ASPECTS score was derived from two independent researchers who were blinded to the patients' clinical status, minimizing individual errors and the risk of misclassification bias. Finally, the development of a web-based calculator facilitates seamless integration of the model into clinical workflows, improving its practicality for bedside use.

However, several limitations should be acknowledged. This single-center retrospective study is prone to selection bias and may limit generalizability. The absence of an external validation cohort raises the potential for overfitting, despite attempts to correct optimism during the internal validation process. Furthermore, the study excluded AIS patients treated with EVT, as logistical

barriers during the study period hindered EVT implementation. This exclusion limits the model's applicability to broader patient populations. Additionally, reliance on 24-h NCCT-ASPECTS precludes the prediction of SAP within the first 24 h of admission, though such early occurrences are rare [41]. Lastly, we acknowledge that conditions such as anemia and chronic inflammation, which can affect RDW measurements, were not considered and may have introduced bias into the results. Due to the retrospective nature of the study, we lacked detailed data on anemia subtypes (e.g., iron deficiency and thalassemia). Anemia, specifically, could confound the RDW-SAP association, as it was not excluded from our analysis and remains a potential limitation. However, a review of our cohort revealed no cases of symptomatic anemia, autoimmune diseases, or chronic inflammatory conditions (e.g., cancer or autoimmune disorders). Future larger multicenter studies with external validation are necessary to confirm these findings and enhance the model's applicability.

Conclusions

This study demonstrated that integrating 24-h NCCT-ASPECTS and RDW into the A^2DS^2 score, along with incorporating non-linear continuous predictors, significantly improves the prediction of SAP in AIS patients treated with thrombolysis. The combined A^2DS^2-MFP model offers excellent discriminative ability and practical utility, providing clinicians with a reliable tool to guide timely interventions. Future work to externally validate this novel model is required to confirm its role in improving early SAP detection, optimizing resource allocation, and ultimately enhancing patient survival.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02282-3.

Additional file 1: Fig. S1 Web application interface for the combined A^2DS^2-MFP calculation, enabling SAP prediction.

Additional file 2: Fig. S2 Web-based application using seven predictors for the combined A^2DS^2-MFP calculation to estimate SAP probability

Additional file 3: Table S1. Cut-off thresholds and predictive values of inflammatory biomarkers from CBC parameters for predicting SAP in thrombolyzed AIS patients. Table S2. Comparison of optimism-adjusted and original performance of the combined A^2DS^2-MFP calculation from bootstrap analysis. Table S3. Final model performance after optimism correction for individual variables. Table S4. Prognostic accuracy of the model for predicting SAP in thrombolyzed AIS patients.

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Author contributions

S.K. wrote the main manuscript text, contributed to the concept and design, and managed data acquisition. S.K. and N.N. conducted the statistical analysis. All authors participated in the interpretation of data. S.K. prepared Figs. 1 and 2, S1, and S2. N.N. prepared Fig. 3. S.K. and N.A. interpreted ASPECTS on NCCT. S.K. wrote the original draft. A.S. and N.N. provided supervision. All authors contributed to the writing review and editing process and reviewed and approved the final manuscript.

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Availability of data and materials

Data are provided within the manuscript (section: Availability of Data and Materials). The datasets generated and/or analyzed during the current study are available in the Open Science Framework repository at https://osf.io/mru7h (https://doi.org/10.17605/OSF.IO/MRU7H).

Declarations

Ethics approval and consent to participate

The Institutional Review Board of Saraburi Hospital granted approval for this study (Certificate No. EC043/2566), which was conducted in accordance with the Declaration of Helsinki (1964) and its subsequent amendments. In consideration of the retrospective design, Saraburi Hospital IRB waived the requirement for obtaining informed consent from each patient.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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