

Development and Validation of a Dynamic Nomogram for Predicting 3-Month Mortality in Acute Ischemic Stroke Patients with Atrial Fibrillation

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Background: Acute ischemic stroke (AIS) in patients with atrial fibrillation (AF) carries a substantial risk of mortality, emphasizing the need for effective risk assessment and timely interventions. This study aimed to develop and validate a practical dynamic nomogram for predicting 3-month mortality in AIS patients with AF.

Methods: AIS patients with AF were enrolled and randomly divided into training and validation cohorts. The nomogram was developed based on independent risk factors identified by multivariate logistic regression analysis. The prediction performance of the nomogram was evaluated using the area under the receiver operating characteristic curve (AUC-ROC), calibration plots, decision curve analysis (DCA), and Kaplan-Meier survival analysis.

Results: A total of 412 patients with AIS and AF entered final analysis, 288 patients in the training cohort and 124 patients in the validation cohort. The nomogram was developed using age, baseline National Institutes of Health Stroke Scale score, early introduction of novel oral anticoagulants, and pneumonia as independent risk factors. The nomogram exhibited good discrimination both in the training cohort (AUC, 0.851; 95% CI, 0.802–0.899) and the validation cohort (AUC, 0.811; 95% CI, 0.706–0.916). The calibration plots, DCA and Kaplan-Meier survival analysis demonstrated that the nomogram was well calibrated and clinically useful, effectively distinguishing the 3-month survival status of patients with AIS and AF, respectively. The dynamic nomogram can be obtained at the website: <https://yanxiaodi.shinyapps.io/3-monthmortality/>.

Conclusion: The dynamic nomogram represents the first predictive model for 3-month mortality and may contribute to managing the mortality risk of patients with AIS and AF.

Keywords: dynamic nomogram, mortality, acute ischemic stroke, atrial fibrillation

Introduction

Stroke, the most common type of which is acute ischemic stroke (AIS), is a major threat to health in China as it is the leading cause of death and the prevalence is on the rise.¹ According to the Global Burden of Disease (GBD) Study 2019, China accounts for 2.19 million of the 6.55 million stroke-related deaths worldwide.² Atrial fibrillation (AF) stands out as a primary risk factor for AIS, significantly elevating the risk of AIS occurrence and associated mortality.^{3,4} Previous studies indicated that patients with AF are five times more likely to experience AIS, often resulting in high mortality within the first 30 days following onset, with figures ranging from 22% to 27%.^{5–7} This represents a substantial public health concern.

While anticoagulant therapy is recommended and acknowledged as an effective approach for reducing mortality in AIS patients with AF, a notable disparity exists between clinical practices and guideline recommendations.^{8–11} Consequently, the potential benefits of lowering mortality risk through anticoagulant therapy have not been fully realized.^{12,13} Therefore, the early identification of factors influencing mortality risk is of paramount importance to facilitate timely interventions and prolong patient longevity.

In the quest for early mortality risk assessment, researchers often turn to predictive models for guidance in treatment and management. Nomograms, as graphical tools, excel in this role by converting relevant risk factors into a continuous scoring system. They enable healthcare professionals to determine precise risk probabilities for specific outcomes in individual patients.^{14,15} In recent times, nomograms have been increasingly applied to predict mortality in stroke patients.^{16–18} Only limited nomograms were established for predicting functional outcome in patients with AIS and AF.^{19,20} However, these previous nomograms were developed based on the baseline characteristics and laboratory indicators, ignoring the important relationship between treatment regimens and mortality. Furthermore, numerous studies have explored mortality risk factors in AIS patients, shedding lights on the intricate interplay of variables.^{21–24} Nevertheless, the exact causes behind the elevated fatality rates in AIS patients with AF, as well as predictive nomograms, remain elusive. In summary, there is an urgent need to identify mortality risk factors and construct predictive nomograms for patients with AIS and AF.

Given the critical significance of accurately predicting mortality to inform sound medical interventions, it becomes imperative to investigate contributing risk factors and develop a user-friendly predictive nomogram. This study aims to construct and validate a practical dynamic nomogram, drawing on multiple independent risk factors, including treatment regimens, to predict 3-month mortality in AIS patients with AF.

Methods

Population and Study Design

This retrospective study was conducted at Nanjing Drum Tower Hospital from January 2019 to December 2021. Patients were enrolled according to the inclusion criteria: (1) diagnosed with AIS and confirmed by cranial computed tomography (CT) or magnetic resonance imaging (MRI) at admission; (2) diagnosed with AF by 24-hour dynamic electrocardiography (ECG) or had an AF history at admission; (3) age ≥ 18 years; (4) obtained the written informed consents. Exclusion criteria were as follows: (1) clinical data missing; (2) length of hospitalization over 1 year; (3) lost to follow-up. This study was conducted in accordance with the Declaration of Helsinki and approved by the Human Ethical Committee and Medical Research Council of Nanjing Drum Tower Hospital (Ethics Number: 2023-026-02). Written informed consents were obtained from all the patients.

Baseline Data Collection

Upon enrollment, patients' characteristics including demographic, medical and medication histories, treatments after onset, stroke-associated infections (including pneumonia and urinary tract infection (UTI)), and baseline laboratory parameters were all collected. The antithrombotic regimens and the initiation time were determined based on the clinicians' expertise in secondary prevention. Other medical interventions aligning with recommendations for stroke secondary prevention. According to the recommendation of the American Heart Association-American Stroke Association (AHA-ASA), the early introduction of NOACs (novel oral anticoagulants) was defined as NOACs treatment commencing within 14 days following AIS.²⁵ Stroke-associated infections were defined as infections diagnosed during hospitalization. Each patient underwent physical examinations conducted by senior clinicians at admission to assess the National Institutes of Health Stroke Scale (NIHSS) score, CHA2DS2-VASc score and HAS-BLED score.

Outcome

The primary outcome was defined as 3-month all-cause mortality following the onset of AIS.^{26,27} Patients were tracked through phone calls or face-to-face interviews until the occurrence of the outcome event or up to 3 months. Patients were

considered lost to follow-up when all follow-up methods failed. Subsequently, patients were categorized into two groups based on their survival status: the death group and the survival group.

Statistical Analysis

Continuous variables with normal distributions were presented as mean $\pm$ standard deviation (SD) and compared using the *t*-test. Non-normally distributed continuous variables were expressed as median (interquartile range, IQR) and analyzed via the Mann–Whitney *U*-test. The chi-square test or Fisher's exact test was used to compare categorical variables, which were presented as frequency (percentage, %). The missing data was generated using the “mice” package by R software.

For the construction and validation of the nomogram, the study population was randomly divided into two cohorts: the training cohort (70%) and the validation cohort (30%). To generate the nomogram for the training cohort, a multivariate logistic regression analysis was performed using a forward stepwise method, incorporating all variables with $P < 0.1$ from univariate logistic regression analysis. Variables with $P < 0.05$ in the multivariate logistic regression analysis along with age (has a well-established association with mortality in stroke patients²⁸) were reserved for nomogram development. The collinearity of variable combinations entered into the multivariate logistic regression analysis was assessed using variance inflation factors (VIF) (< 2 considered not significant). The baseline CHA2DS2-VASc score was excluded from the multivariate logistic regression analysis, as it is calculated from age and medical histories. Regression coefficients and odds ratios (OR) with two-sided 95% confidence intervals (CI) were calculated for each variable in the model.

Discrimination of the nomogram was assessed using the area under the receiver operating characteristic curve (AUC-ROC). Calibration of the nomogram was evaluated by plotting the concordance between actual and predicted risk of 3-month mortality and applying the Hosmer-Lemeshow test ($P > 0.05$). Clinical validity of the nomogram was assessed through decision curve analysis (DCA) by calculating the net benefit for a range of threshold probabilities. For further validation, an optimal cutoff value derived from the risk score in the training cohort was used to stratify patients into low-risk and high-risk groups. Subsequently, survival analysis was conducted by plotting Kaplan-Meier curves with Log rank tests to compare survival distributions between the low-risk and high-risk groups.

The statistical analyses were performed using STATA 17.0 (Stata Corporation, College Station, Texas) and R software (version 4.0.3). Statistical significance was defined as two-tailed $P < 0.05$.

Results

Baseline Characteristics

From January 2019 to December 2021, a total of 431 AIS patients with AF were enrolled in this study. After the exclusion of 19 patients, including 1 with clinical data missing, 3 with hospitalization over 1 year, and 15 lost to follow-up, a cohort of 412 patients were eligible for analysis. After random allocation, 288 patients comprised in the training cohort, and 124 patients formed the validation cohort (Figure 1).

Table 1 presented the baseline characteristics of patients in both the training and validation cohorts. Among 412 patients, 209 (50.7%) were males, and the median age was 80 years. A total of 88 (21.4%) patients died within 3 months after onset. During hospitalization, 146 (35.4%) patients developed pneumonia. Notably, the training cohort exhibited a higher incidence of pneumonia compared to the validation cohort (38.9% vs 27.4%, $P = 0.026$). All other baseline characteristics and outcomes were well-balanced between the two cohorts (all $P > 0.05$).

There were 66 (22.9%) patients and 22 (17.7%) patients dead in the training and validation cohorts, respectively. Table 2 demonstrated that patients in the death group were older and had higher baseline NIHSS score (all $P < 0.05$). Pneumonia was notably more prevalent in the death group than in the survival group, both in the training and validation cohorts ($P < 0.001$). In the training cohort, patients in the death group exhibited lower total cholesterol levels ($P = 0.016$) and received thrombectomy therapy more frequently ($P < 0.001$) than those in the survival group. Conversely, more patients in the survival group reported a history of drinking and received early introduction of NOACs (all $P < 0.05$). In the validation cohort, the prevalence of hypertension was higher in the death group compared to the survival group ($P = 0.047$).

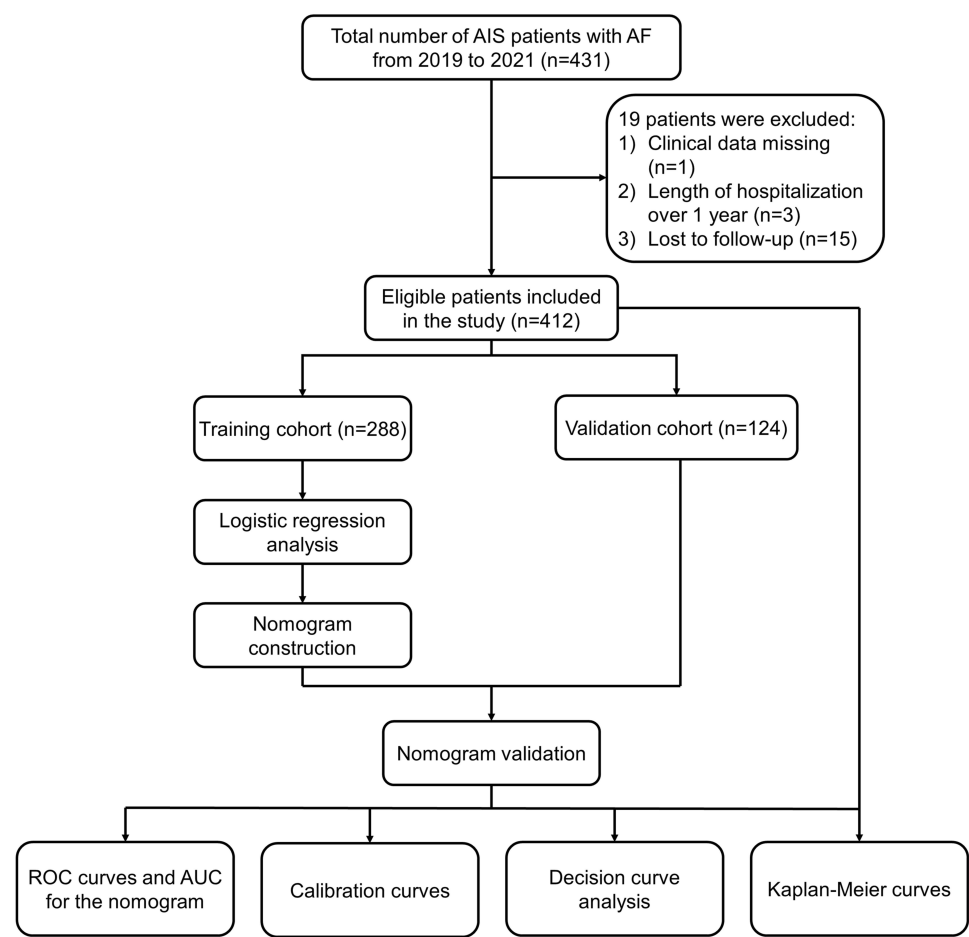


Figure 1 Flow diagram of the study.
Abbreviations: AIS, acute ischemic stroke; AF, atrial fibrillation; ROC, receiver operating characteristic; AUC, area under the ROC curve.

Predictive Nomogram Development

Univariate and multivariate logistic regression analysis were performed to identify risk factors for 3-month mortality in the training cohort (Table 3, [Supplementary Table 1](#)). No significant statistical collinearity was observed (all VIF <2)

Table 1 Comparison of Baseline Characteristics Between the Training and Validation Cohorts

Variables	Total (n=412)	Training Cohort (n=288)	Validation Cohort (n=124)	P value
Demographics				
Male, n (%)	209 (50.7)	146 (50.7)	63 (50.8)	0.983
Age, years, median (IQR)	80.0 (71.0–85.0)	79.0 (70.8–85.0)	81.0 (73.5–86.0)	0.162
Smoking, n (%)	25 (6.1)	42 (14.6)	21 (16.9)	0.543
Drinking, n (%)	50 (12.1)	32 (11.1)	18 (14.5)	0.332
Medical history, n (%)				
Hypertension	299 (72.6)	214 (74.3)	85 (68.5)	0.230
Diabetes mellitus	113 (27.4)	71 (24.7)	42 (33.9)	0.054
Heart failure	48 (11.7)	33 (11.5)	15 (12.1)	0.853
Stroke/TIA	152 (36.9)	103 (35.8)	49 (39.5)	0.469

(Continued)

Table 1 (Continued).

Variables	Total (n=412)	Training Cohort (n=288)	Validation Cohort (n=124)	P value
Medication history, n (%)				
Antithrombotic drugs	160 (38.8)	116 (40.3)	44 (35.5)	0.360
Antihypertensive drugs	273 (66.3)	195 (67.7)	78 (62.9)	0.344
Diuretics	21 (5.1)	14 (4.9)	7 (5.6)	0.740
Baseline score, median (IQR)				
NIHSS score	8.0 (2.0–15.0)	7.5 (2.0–15.0)	8.0 (2.0–13.5)	0.787
CHA2DS2-VASc score	4.0 (3.0–6.0)	4.0 (3.0–6.0)	5.0 (4.0–6.0)	0.237
HAS-BLED score	2.0 (1.0–3.0)	2.0 (1.0–2.0)	2.0 (1.0–3.0)	0.936
Treatment after onset, n (%)				
Thrombolytic therapy	94 (22.8)	71 (24.7)	23 (18.5)	0.176
Thrombectomy therapy	106 (25.7)	82 (28.5)	24 (19.4)	0.052
Early introduction of NOACs	139 (33.7)	93 (32.3)	46 (37.1)	0.344
Stroke-associated infection, n (%)				
Pneumonia	146 (35.4)	112 (38.9)	34 (27.4)	0.026
UTI	29 (7.0)	22 (7.6)	7 (5.6)	0.468
Baseline laboratory parameters				
WBC, $\times 10^9/L$, median (IQR)	7.6 (6.1–9.6)	7.6 (6.2–9.5)	7.1 (5.7–10.2)	0.282
RBC, $\times 10^{12}/L$, median (IQR)	4.4 (4.0–4.7)	4.4 (4.0–4.8)	4.3 (3.9–4.6)	0.089
PLT, $\times 10^9/L$, median (IQR)	172.0 (140.0–217.0)	173.5 (143.5–218.5)	165.0 (129.0–214.0)	0.060
TG, mmol/L, median (IQR)	0.9 (0.7–1.4)	1.0 (0.8–1.4)	0.8 (0.7–1.1)	0.353
TC, mmol/L, median (IQR)	4.0 (3.4–4.8)	4.2 (3.4–4.8)	3.9 (3.2–4.7)	0.605
eGFR, mL/min/1.73m ² , mean $\pm$ SD	89.5 $\pm$ 26.3	89.5 $\pm$ 26.3	89.4 $\pm$ 26.3	0.977
PT, s, median (IQR)	12.1 (11.4–12.9)	12.1 (11.4–12.8)	12.1 (11.4–13.6)	0.400
APTT, s, median (IQR)	26.4 (24.9–28.2)	26.3 (24.9–28.1)	26.9 (25.1–28.5)	0.467
TT, s, median (IQR)	18.2 (17.5–19.1)	18.3 (17.5–18.9)	18.2 (17.0–19.4)	0.773
FIB, g/L, median (IQR)	3.0 (2.5–3.5)	3.0 (2.5–3.5)	3.0 (2.5–3.4)	0.370
D-dimer, mg/L, median (IQR)	1.0 (0.5–2.2)	1.0 (0.5–2.1)	1.1 (0.5–2.4)	0.211
Status, n (%)				
Death	88 (21.4)	66 (22.9)	22 (17.7)	0.240
Survival	324 (78.6)	222 (77.1)	102 (82.3)	

Abbreviations: SD, standard deviation; IQR, interquartile range; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; NOACs, novel oral anticoagulants; UTI, urinary tract infection; WBC, white blood cell; RBC, red blood cell; PLT, platelet count; TG, triglyceride; TC, total cholesterol; eGFR, estimated glomerular filtration rate; PT, prothrombin time; APTT, activated partial prothrombin time; TT, thrombin time; FIB, fibrinogen.

Table 2 Comparison of Baseline Characteristics Between the Death and Survival Groups in the Training and Validation Cohorts

Variables	Training Cohort (n=288)			Validation Cohort (n=124)		
	Death (n=66)	Survival (n=222)	P value	Death (n=22)	Survival (n=102)	P value
Demographics						
Male, n (%)	28 (42.4)	118 (53.2)	0.126	10 (45.5)	53 (52.0)	0.580
Age, years, median (IQR)	83.0 (73.0–87.0)	77.0 (70.0–83.5)	0.002	86.0 (82.0–86.0)	79.0 (71.8–86.3)	0.010
Smoking, n (%)	8 (12.1)	34 (15.3)	0.519	1 (4.5)	20 (19.6)	0.088
Drinking, n (%)	2 (3.0)	30 (13.5)	0.017	1 (4.5)	17 (16.7)	0.143
Medical history, n (%)						
Hypertension	51 (77.3)	163 (73.4)	0.530	19 (86.4)	66 (64.7)	0.047
Diabetes mellitus	19 (28.8)	52 (23.4)	0.375	11 (50.0)	31 (30.4)	0.078
Heart failure	9 (13.6)	24 (10.8)	0.527	4 (18.2)	11 (10.8)	0.335
Stroke/TIA	25 (37.9)	78 (35.1)	0.683	9 (40.9)	40 (39.2)	0.883

(Continued)

Table 2 (Continued).

Variables	Training Cohort (n=288)			Validation Cohort (n=124)		
	Death (n=66)	Survival (n=222)	P value	Death (n=22)	Survival (n=102)	P value
Medication history, n (%)						
Antithrombotic drugs	27 (40.9)	89 (40.1)	0.905	11 (50.0)	33 (32.4)	0.117
Antihypertensive drugs	46 (69.7)	149 (67.1)	0.694	17 (77.3)	61 (59.8)	0.124
Diuretics	1 (1.5)	13 (5.9)	0.150	2 (9.1)	5 (4.9)	0.440
Baseline score, median (IQR)						
NIHSS score	16.0 (11.5–21.5)	5.0 (2.0–11.0)	<0.001	16.0 (11.0–24.0)	5.0 (1.0–11.5)	<0.001
CHA2DS2-VASc score	5.0 (3.5–6.0)	4.0 (3.0–5.5)	0.076	5.0 (4.0–6.0)	5.0 (4.0–6.0)	0.114
HAS-BLED score	2.0 (1.0–2.5)	2.0 (1.0–2.0)	0.591	3.0 (2.0–3.0)	2.0 (1.0–2.3)	0.147
Treatment after onset, n (%)						
Thrombolytic therapy	14 (21.2)	57 (25.7)	0.460	4 (18.2)	19 (18.6)	0.961
Thrombectomy therapy	30 (45.5)	52 (23.4)	<0.001	6 (27.3)	18 (17.6)	0.300
Early introduction of NOACs	5 (7.6)	88 (39.6)	<0.001	5 (22.7)	41 (40.2)	0.124
Stroke-associated infection, n (%)						
Pneumonia	49 (74.2)	63 (28.4)	<0.001	15 (68.2)	19 (18.6)	<0.001
UTI	4 (6.1)	18 (8.1)	0.582	2 (9.1)	5 (4.9)	0.440
Baseline laboratory parameters						
WBC, $\times 10^9/L$, median (IQR)	8.5 (6.0–10.8)	7.5 (6.3–9.3)	0.433	6.2 (4.5–11.6)	7.2 (6.0–10.2)	0.930
RBC, $\times 10^{12}/L$, median (IQR)	4.3 (3.8–4.7)	4.5 (4.1–4.9)	0.091	4.6 (3.8–4.9)	4.3 (3.9–4.5)	0.127
PLT, $\times 10^9/L$, median (IQR)	167.0 (146.5–207.5)	176.0 (140.5–225.5)	0.502	134.0 (111.0–199.0)	169.0 (133.0–217.5)	0.766
TG, mmol/L, median (IQR)	1.0 (0.7–1.5)	1.0 (0.8–1.4)	0.880	1.0 (0.8–1.5)	0.8 (0.7–1.1)	0.999
TC, mmol/L, median (IQR)	3.7 (3.2–4.5)	4.2 (3.5–4.9)	0.016	4.8 (3.2–5.3)	3.8 (3.2–4.5)	0.593
eGFR, mL/min/1.73m ² , mean $\pm$ SD	91.6 $\pm$ 26.7	88.9 $\pm$ 26.2	0.460	85.8 $\pm$ 19.5	90.2 $\pm$ 27.5	0.491
PT, s, median (IQR)	11.9 (11.5–12.5)	12.1 (11.4–12.9)	0.118	11.4 (10.8–12.8)	12.3 (11.5–13.8)	0.555
APTT, s, median (IQR)	26.3 (24.7–27.5)	26.3 (24.9–28.3)	0.148	27.3 (27.1–28.4)	26.6 (25.0–28.6)	0.242
TT, s, median (IQR)	18.3 (17.6–19.1)	18.2 (17.5–18.9)	0.999	18.3 (17.5–19.2)	18.2 (16.9–19.4)	0.704
FIB, g/L, median (IQR)	3.0 (2.5–3.5)	2.9 (2.5–3.6)	0.826	3.2 (2.9–3.7)	3.0 (2.5–3.4)	0.885
D-dimer, mg/L, median (IQR)	1.5 (0.8–2.5)	0.9 (0.4–2.1)	0.199	1.0 (0.4–2.4)	1.3 (0.5–2.5)	0.950

Abbreviations: SD, standard deviation; IQR, interquartile range; TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; NOACs, novel oral anticoagulants; UTI, urinary tract infection; WBC, white blood cell; RBC, red blood cell; PLT, platelet count; TG, triglyceride; TC, total cholesterol; eGFR, estimated glomerular filtration rate; PT, prothrombin time; APTT, activated partial prothrombin time; TT, thrombin time; FIB, fibrinogen.

Table 3 Univariate and Multivariate Logistic Regression Analysis for the Risk Factors Associated with 3-Month Mortality in the Training Cohort

Variables	Univariate Analysis			Multivariate Analysis		
	VIF	OR (95% CI)	P value	Regression Coefficient (SE)	aOR (95% CI)	P value
Age	1.17	1.05 (1.02–1.09)	0.001	0.03 (0.02)	1.03 (0.99–1.07)	0.130
Drinking	1.12	0.20 (0.05–0.86)	0.031			
NIHSS score	1.77	1.14 (1.10–1.18)	<0.001	0.08 (0.02)	1.09 (1.04–1.13)	<0.001
Thrombectomy therapy	1.42	2.72 (1.53–4.84)	0.001			
Early introduction of NOACs	1.12	0.12 (0.05–0.32)	<0.001	−1.36 (0.51)	0.26 (0.09–0.71)	0.008
Pneumonia	1.37	7.27 (3.90–13.58)	<0.001	1.14 (0.36)	3.13 (1.54–6.38)	0.002
TC	1.06	0.72 (0.53–0.97)	0.033			
APTT	1.08	0.92 (0.84–1.01)	0.067			

Abbreviations: OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; VIF, variance inflation factors; SE, standard error; NIHSS, National Institutes of Health Stroke Scale; NOACs, novel oral anticoagulants; TC, total cholesterol; APTT, activated partial prothrombin time.

among the variables in the univariate logistic regression analysis. After adjusting for all confounders, age (adjusted odds ratio [aOR], 1.03; 95% CI, 0.99–1.07; $P=0.130$), baseline NIHSS score (aOR, 1.09; 95% CI, 1.04–1.13; $P<0.001$), early introduction of NOACs (aOR, 0.26; 95% CI, 0.09–0.71; $P=0.008$), and pneumonia (aOR, 3.13; 95% CI, 1.54–6.38; $P=0.002$) emerged as independent clinical predictors of 3-month mortality.

The predictive dynamic nomogram was subsequently developed based on these independent predictors (Figure 2A). To acquire the matching points on the “Points” scale, each predictor was highlighted on the nomogram, and a vertical line was drawn to the “Points” axis. The points of each predictor were summed to generate the total points, which was then located on the “Total points” axis to estimate the probability of 3-month mortality. Increasing total points in the nomogram were associated with a higher likelihood of 3-month mortality, while decreasing total points were related to a lower risk of 3-month mortality. The dynamic nomogram with an intuitive web-based interface was also developed so as to facilitate the use for clinicians in clinical practices (Figure 2B) (Dynamic Nomogram: <https://yanxiaodi.shinyapps.io/3-monthmortality/>).

Nomogram Validation

The discriminative capacity of the nomogram was verified based on the AUC values. The AUC values of the training (Figure 3A) and validation (Figure 3B) cohorts were 0.851 (95% CI, 0.802–0.899) and 0.811 (95% CI, 0.706–0.916),

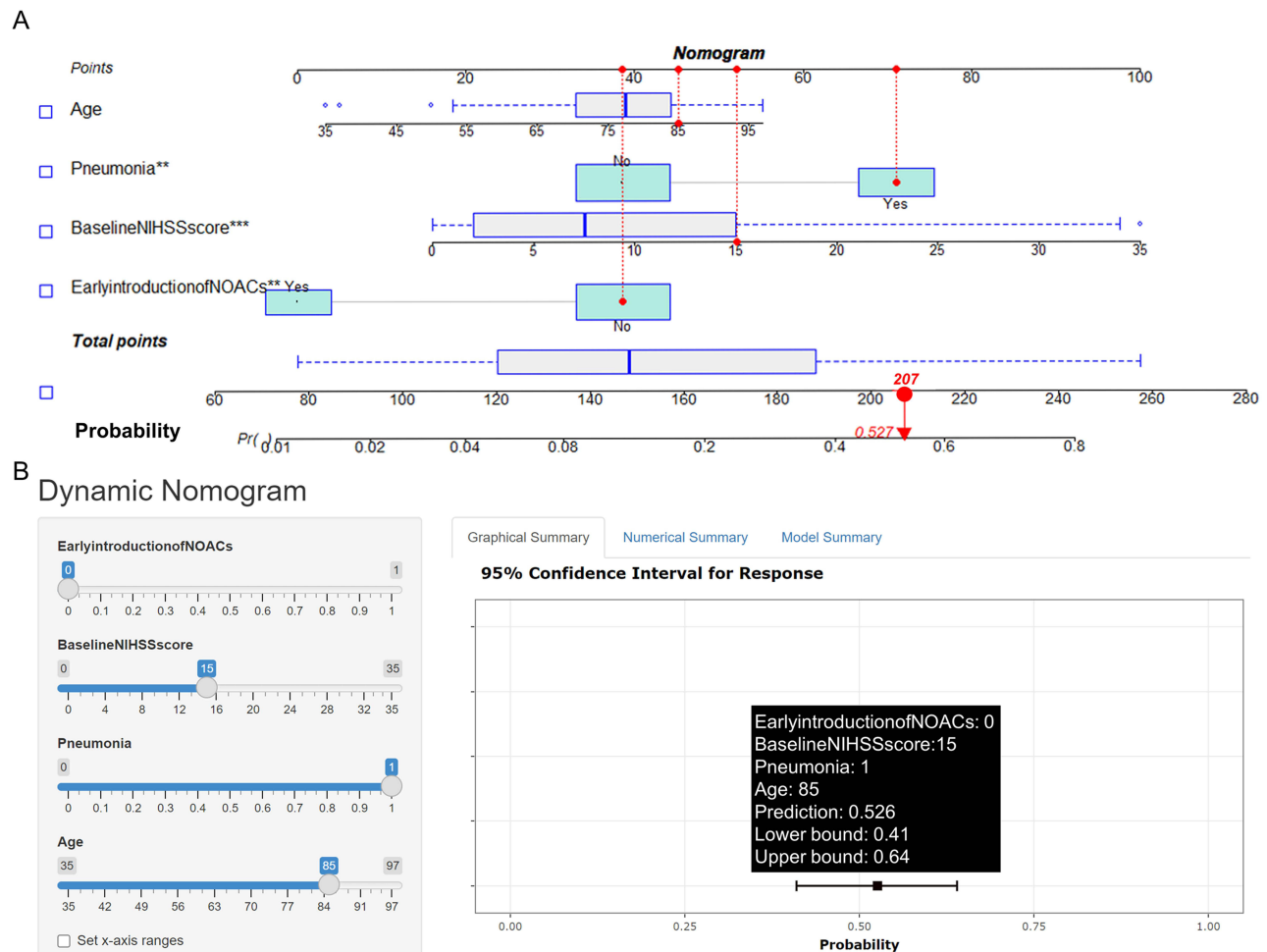


Figure 2 Dynamic nomogram for prediction of 3-month mortality in patients with AIS and AF. **(A)** The dynamic nomogram. Points were assigned to each predictor by drawing a vertical line to the “Points” axis and then calculated the total points as the sum of them. The probability of 3-month mortality can be easily obtained according to the total points. The example of using the nomogram was based on an 85-year-old patient, whose baseline NIHSS score was 15, got pneumonia, and without early introduction of NOACs, the probability of 3-month mortality was 52.7%. **(B)** The intuitive interface of the online dynamic nomogram (<https://yanxiaodi.shinyapps.io/3-monthmortality/>). **: $P<0.05$; ***: $P<0.001$.

Abbreviations: NOACs, novel oral anticoagulants; NIHSS, National Institutes of Health Stroke Scale; AIS, acute ischemic stroke; AF, atrial fibrillation.

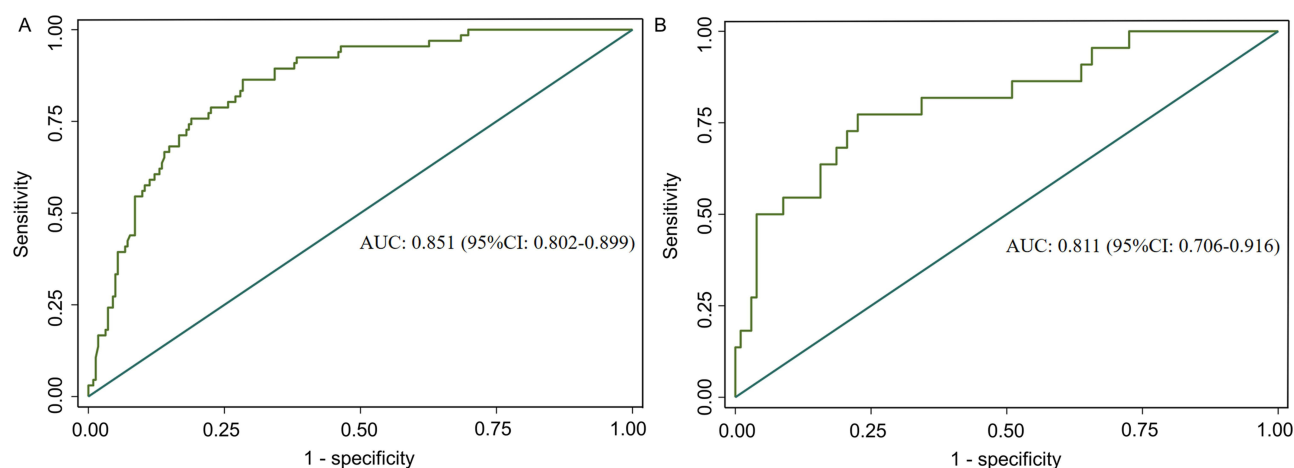


Figure 3 ROC curves of the nomogram for predicting 3-month mortality in patients with AIS and AF. **(A)** ROC curve of the training cohort; **(B)** ROC curve of the validation cohort.

Abbreviations: ROC, receiver operating characteristic; AUC, area under the ROC curve; AIS, acute ischemic stroke; AF, atrial fibrillation.

respectively, demonstrating that the established nomogram performed well. The optimal cutoff values of the training and validation cohorts were 0.790 (sensitivity, 86%; specificity, 72%) and 0.770 (sensitivity, 77%; specificity, 77%), respectively. Using the optimal cutoff value from the training cohort, patients in the training cohort, validation cohort and complete set were stratified into low-risk (below cutoff) and high-risk (above cutoff) groups. Kaplan-Meier survival curves revealed significantly lower 3-month mortality in the low-risk group compared to the high-risk group (all $P < 0.001$) in the training cohort (Figure 4A), validation cohort (Figure 4B), and complete set (Figure 4C).

The calibration plots demonstrated high concordance between the predicted and actual probabilities of 3-month mortality both in the training ($\chi^2=8.74$, $P=0.557$) (Figure 5A) and validation ($\chi^2=5.21$, $P=0.877$) (Figure 5B) cohorts,

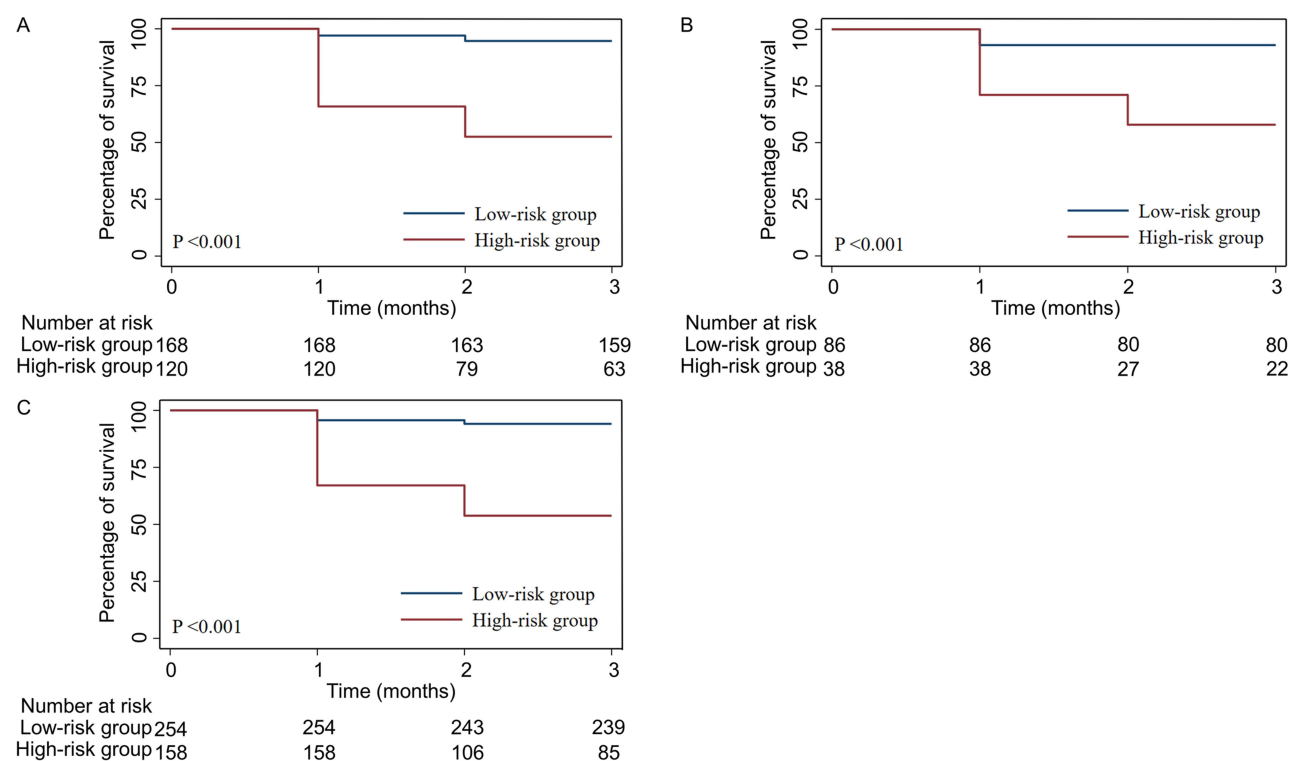


Figure 4 Kaplan-Meier survival curves of patients in the low-risk and high-risk groups. **(A)** Training cohort; **(B)** Validation cohort; **(C)** Complete set.

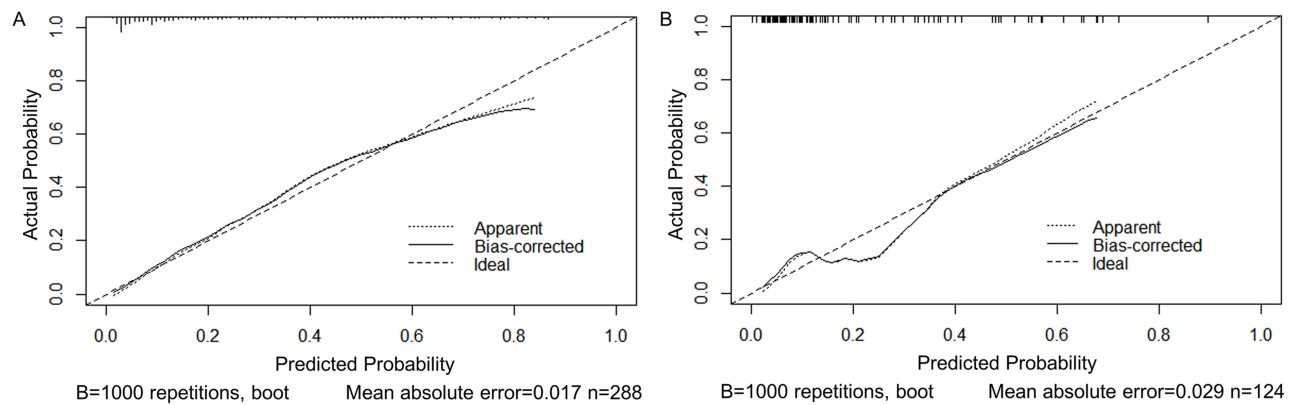


Figure 5 Calibration plots of the nomogram in the training (A) and validation (B) cohorts.

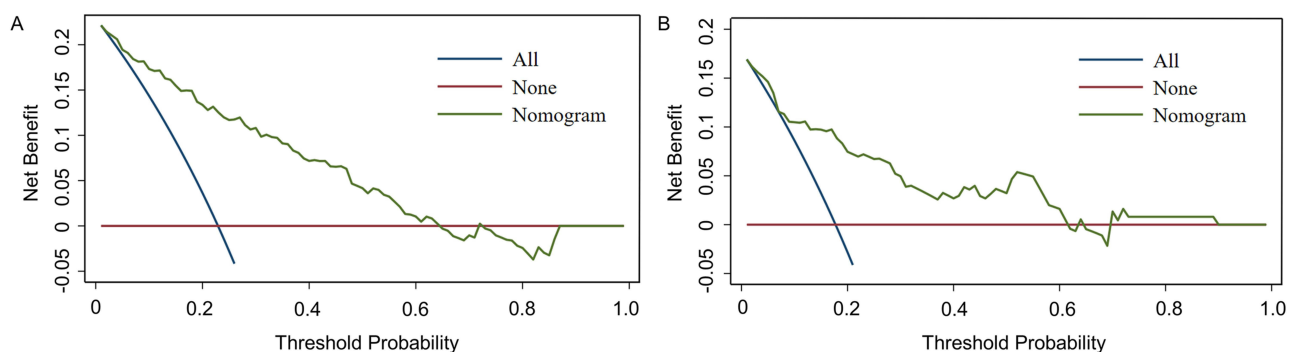


Figure 6 Decision curve analysis for the training cohort (A) and the validation cohort (B).

signifying strong agreement between predicted and observed outcomes. The mean absolute errors of the calibration in training and validation cohorts, calculated via bootstrapping (resampling = 1000), were 0.017 and 0.029, respectively.

The clinical validity of the nomogram was further confirmed through DCA. The results indicated a substantial net benefit of the nomogram in predicting 3-month mortality in patients with AIS and AF across a range of threshold probability, spanning from 2% to 64% in the training cohort (Figure 6A) and 3% to 61% in the validation cohort (Figure 6B).

Discussion

In this study, we developed and validated a novel and practical dynamic nomogram for predicting 3-month mortality in patients with AIS and AF. The nomogram incorporated independent risk factors, including age, baseline NIHSS score, early introduction of NOACs, and pneumonia. The robust discriminative capacity of the nomogram, as evidenced by the AUC values and Kaplan-Meier survival analysis findings, suggested its potential to accurately predict 3-month survival in AIS patients with AF. Additionally, the nomogram demonstrated stability and reliability both in the training and validation cohorts, as indicated by the calibration plots. Moreover, the DCA results underscored the practicality and clinical applicability of the nomogram in identifying and managing the risk of 3-month mortality in patients with AIS and AF.

Our findings were consistent with previous studies, highlighted age and NIHSS score as primary independent risk factors for short- and long-term mortality in patients with ischemic stroke (IS) and AF.^{29–33} Age is closely intertwined with stroke incidence and severity.³⁴ Previous researches reported that the mortality of patients with stroke rose with age.^{35,36} This condition may be caused by the fact that elderly patients often present with more comorbidities and poorer outcomes. Additionally, aging is associated with chronic inflammation and ischemic brain damage, both contributing to

worse prognosis in stroke patients.^{37,38} Stroke severity, as assessed by the NIHSS score, is a critical determinant of post-stroke mortality.^{39–41} Besides, higher baseline NIHSS scores indicate severe neurological deficits, which are associated with an increased risk of mortality in IS patients.^{42–44} Therefore, the inclusion of age and baseline NIHSS score in our nomogram aligns with the established studies and strengthens its predictive capabilities.

Stroke-associated infections, particularly pneumonia, which accounts for 11.3% to 31.3% of all stroke-associated infections and arises virtually after stroke, represent a common complication in stroke patients.^{45,46} Traditionally, impaired levels of consciousness and severe dysphagia are considered as related risk factors for aspiration in stroke patients, leading to pneumonia.^{47,48} Moreover, patients experiencing an acute stroke are more susceptible to infections due to the systemic immunodepression, primarily triggered by excessive stimulation of the autonomous nervous system.⁴⁹ In medical practice, the risk of mortality associated with pneumonia remains a significant concern for stroke patients. It has been reported that pneumonia can lead to an increase ranging in short-term mortality from 10.1% to 37.3% and in long-term mortality from 49.0% to 60.1% following AIS.^{50–52} The association between pneumonia and the increased risk of mortality has been well-documented, emphasizing the importance of monitoring and managing pneumonia in AIS patients with AF. Therefore, our inclusion of pneumonia as an independent predictor in the nomogram aligns with the clinical reality and enhances its prognostic accuracy.

AF predisposes patients to thromboembolic events by pooling blood in the atria, making anticoagulant therapy a critical component of stroke prevention.⁵³ Both warfarin and NOACs have demonstrated their efficacy in reducing mortality among stroke patients with AF by inhibiting clot formation.^{54–58} Notably, both North American and European guidelines recommend anticoagulant therapy for stroke prevention in AF patients, favoring it over antiplatelet therapy.⁵⁹ NOACs have shown superiority over warfarin in terms of both efficacy and safety in preventing stroke in AF patients. The ARISTOPHANES study, the largest observation study on NOACs and warfarin to date, found that NOACs significantly lower the risk of stroke/systemic embolism compared to warfarin in AF patients.⁶⁰ However, the efficacy of early and delay NOACs treatment in patients with AIS and AF remains controversial. The definitions of early and delay NOACs treatment also vary among different studies. For instance, the TIMING study showed that early NOACs treatment (≤ 4 days) was noninferior to delay NOACs treatment (5–10 days) in reducing the risk of 90-day mortality in patients with AIS and AF.⁶¹ Similarly, Wilson et al found no significant difference in 90-day mortality between patients receiving early (≤ 4 days) and delayed (≥ 5 days) anticoagulant therapy in an observational study based on the data from CROMIS-2 study.⁶² In contrast, the RELAXED study reported that AIS patients with AF who initiated rivaroxaban within 14 days had a lower incidence of 90-day mortality compared to those started rivaroxaban ≥ 15 days after onset.⁶³ These varying findings highlight the ongoing controversy surrounding the optimal timing of NOACs initiation in this patient population. Our study investigated the impact of the timing of NOACs initiation on 3-month mortality and revealed a significant association between early NOACs introduction (within 14 days) and reduced 3-month mortality. This finding provides valuable insights into the timing of anticoagulant therapy initiation in these high-risk patients.

The nomogram is regarded as a crucial decision-making prediction tool for investigating the relationship between the prognosis and baseline status.^{64,65} Previous nomograms designed to predict outcomes typically relied on baseline characteristics or predefined treatment regimens, often overlooking the impact of anticoagulant therapy on prognosis.^{66,67} For instance, Cappellari et al constructed a nomogram to predict functional outcomes based on the AF patients who received NOACs within 7 days after stroke.²⁰ However, their study failed to explain the relationship between delayed NOACs treatment and functional outcomes or mortality. Our study developed a nomogram with favorable predictive capabilities, taking into account the significant influence of early introduction of NOACs on 3-month mortality. To the best of our knowledge, our study's nomogram represents the first model tailored for predicting 3-month mortality in patients with AIS and AF. Early identification of mortality risk factors is paramount for enabling timely interventions. For instance, early assessment of NIHSS score increases the likelihood of detecting symptomatic fluctuations and enables more effective interventions to improve outcomes.^{68,69} Besides, patients have the potential to have better prognosis and lower mortality risk by minimizing the occurrence of pneumonia and treating with early NOACs therapy.^{9,10,47} Consequently, our dynamic nomogram is designed to be practical, reliable, and user-friendly. We established it based on readily available factors during hospitalization, offering clinicians valuable guidance for implementing early interventions to prevent pneumonia and administer anticoagulant therapy.

There were several limitations in our study. Firstly, this is a single-center retrospective study, which may limit the statistical power of the results. Secondly, the training cohort and the validation cohort had a significant difference in pneumonia, thus, further research centers and external validation are necessary to confirm the clinical utility and performance of the nomogram. Thirdly, our study did not include a comparative analysis of laboratory test results during follow-up. Despite these limitations, our study has successfully identified important 3-month mortality risk factors in patients with AIS and AF. Furthermore, the dynamic nomogram serves as a valuable tool for increasing the proportion of patients receiving early introduction of NOACs, ultimately improving the clinical outcomes of individuals with AIS and AF.

Conclusion

In summary, this study is the first attempt to develop and validate a user-friendly clinical dynamic nomogram, incorporating independent risk factors, for the prediction of 3-month mortality in patients with AIS and AF. This dynamic nomogram holds the potential to aid in the assessment of an individual's 3-month mortality risk and serves as a compass for guiding future treatments aimed at prolonging the survival time of high-risk patients.

Abbreviations

GBD, Global Burden of Disease; AF, atrial fibrillation; AIS, acute ischemic stroke; CT, computed tomography; MRI, magnetic resonance imaging; ECG, electrocardiography; UTI, urinary tract infection; AHA-ASA, American Heart Association-American Stroke Association; NOACs, novel oral anticoagulants; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; IQR, interquartile range; VIF, variance inflation factor; OR, odds ratio; CI, confidence interval; AUC-ROC, area under the receiver operating characteristic curve; DCA, decision curve analysis; aOR, adjusted Odds Ratio; IS, ischemic stroke.

Data Sharing Statement

Data presented in the study are included in the article. Data will be made available on request by contacting the corresponding authors.

Ethics Approval and Informed Consent

Ethical approval to report this work was obtained from the Ethics Committee of Nanjing Drum Tower Hospital (Ethics Number: 2023-026-02). Written informed consent was obtained from the patients for their anonymized information to be published in this article.

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Author Contributions

All authors made substantial contributions to conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting the article or critically revising for important intellectual content; gave final approval of the version to be published; agreed to submit to the current journal; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflict of interest in this work.

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