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Development and validation of a machine learning-based model for postoperative ischemic stroke in middle-aged and elderly patients with hip or knee arthroplasty

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Abstract

Postoperative ischemic stroke in middle-aged and elderly patients with hip or knee arthroplasty remains a major postoperative challenge, little is known about its incidence and risk factors. This study sought to create a nomogram for precise prediction of ischemic stroke after hip or knee arthroplasty.

Discharge data of all middle-aged and elderly patients undergoing primary hip or knee arthroplasty from May 2013 to October 2020 were queried. These patients were then followed up over time to determine their risk of ischemic stroke. Clinical parameters and blood biochemical features were analyzed by the use of univariable and multivariable generalized logistic regression analysis. A nomogram to predict the risk of ischemic stroke was constructed and validated with bootstrap resampling.

Eight hundred twenty-eight patients were included for analysis; Fifty-one were diagnosed with ischemic stroke. After final regression analysis, age, the neutrophil-to-lymphocyte ratio (NLR), a standard deviation of red blood cell distribution width, American Society of Anesthesiologists, low-density lipoprotein, and diabetes were identified and were entered into the nomogram. The nomogram showed an area under the receiver operating characteristic curve of 0. 841 (95% confidence interval [CI], 0.809–0.871). The calibration curves for the probability of ischemic stroke showed optimal agreement between the probability as predicted by the nomogram and the actual probability (Hosmer-Lemeshow test: P = .818).

We developed a practical nomogram that can predict the risk of ischemic stroke for middle-aged and elderly patients with hip or knee arthroplasty. This model has the potential to assist clinicians in making treatment recommendations.

Abbreviations: ASA = American Society of Anesthesiologists, LC = Lymphocyte count, LDL-C = low-density lipoprotein, PLT = blood platelet, RDW-SD = Standard deviation of red blood cell distribution width, Scr = serum creatinine.

Keywords: ischemic stroke, nomogram, predictive model, risk factors, hip or knee arthroplasty

1. Introduction

Stroke (ischemic stroke or hemorrhagic stroke) is the leading cause of disability and the second leading cause of death worldwide.[1] Ischemic stroke in most cases is caused due to an abrupt blockage of an artery, but in some instances, hemorrhagic stroke may be caused due to bleeding into brain tissue when a blood vessel ruptures.[1,2]

Of note, stroke is one of the most devastating complications of bone fracture, occurring in up to 4% of patients after surgical repair for hip fracture.[3] Ischemic stroke is a major health issue in middle-aged and elderly patients with hip or knee arthroplasty and leads to increased functional disability and reduced quality of life.[4] Hence, clarifying the risk of ischemic stroke after hip or knee arthroplasty may benefit patient care by enabling patient counseling and by promoting strategies to prevent this disabling complication in stroke survivors.

Currently, there is no optimal strategy for prevention or treatment of post-stroke bone fracture or post-bone fracture stroke.[3] For most individuals who have not received thrombolysis, anticoagulation, or antiplatelet, therapy is recommended to decrease the incidence of recurrent stroke.[5,6] However, these therapies inevitably increase the incidence of bone fracture hemorrhage, and there are no guidelines on the use of antithrombotic drugs

This study was approved by the Ethics Committee and Institutional Review Board of the The First People's Hospital of Linping District (Reference: 2021HGR-021).

Informed consent was not applicable.

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The datasets generated during and/or analyzed during the current study are publicly available.

All procedures performed in studies involving human participants were following the ethical standards of the institutional and national research committee and with the Helsinki declaration. This study was approved by the Ethics Committee and Institutional Review Board of the First People's Hospital of Linping District (Reference: 2021HGR-021).

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for these patients with bone fracture.[7] Therefore, new reliable methods for the preoperative prediction of ischemic stroke are highly required.

In this study, we developed a nomogram based on variables of routine examinations that were able to predict the probability of postoperative ischemic stroke in middle-aged and elderly patients with hip or knee arthroplasty. We then analyzed the predictive performance of this nomogram in a deviation cohort and then verified performance in an internal validation cohort.

2. Methods

2.1. Patients collection

Between May 2013 to October 2020, we prospectively collated data from consecutive patients who had received hip or knee arthroplasty at The First People's Hospital of Linping District. This study was approved by the Institutional Ethics Committee of the The First People's Hospital of Linping District (Reference: 2021HGR-021), compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants before any treatment. All patients' information was anonymous. The inclusion and exclusion criteria were summarized in Figure 1. Eligible patients who received hip or knee arthroplasty were included in the training cohort so that we could establish the generalized linear-based models.

2.2. Clinical data extraction

The data of patients were collected, including: (1) general information before operation, such as age, venereal disease, weight, height, systolic blood pressure, diastolic blood pressure, American Society of Anesthesiology classification, past medical history, etc. (2) Preoperative blood routine indicators, such as white blood cell count, platelet count, red blood cell count, red blood cell distribution width, hematocrit, hemoglobin, etc. (3) Preoperative blood biochemical indexes, such as albumin, fasting blood glucose, uric acid, creatinine, total

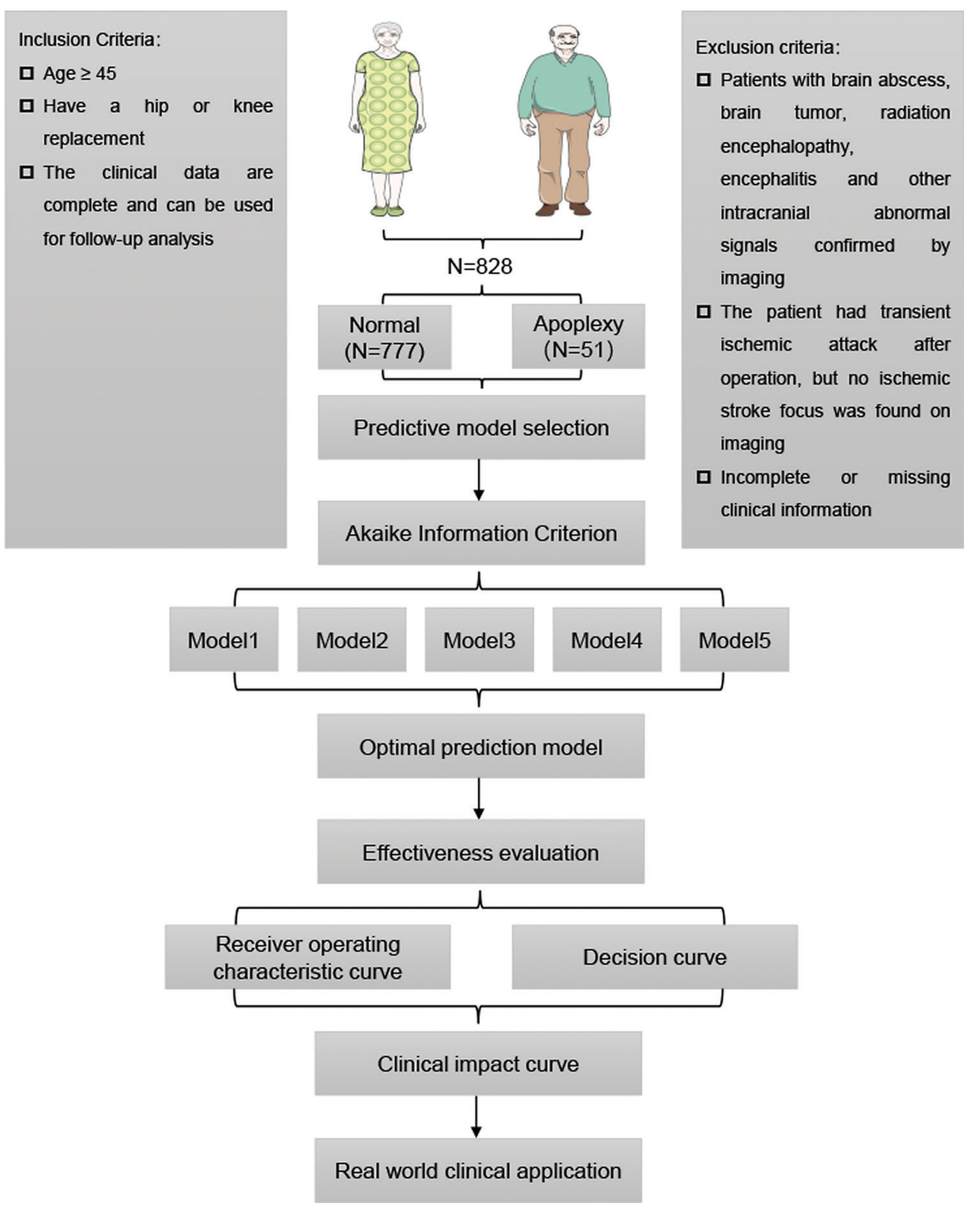

Figure 1. The flow chart of patient selection and data process.

cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, etc.

2.3. Diagnostic criteria of ischemic stroke

The diagnostic criteria of ischemic stroke are as follows: (1). The patient showed acute onset; (2). The patients presented with focal neurological deficit (such as weakness or numbness of one side of the face or limb, language disorder, etc.), and a few patients presented with comprehensive neurological deficit; (3). The duration of symptoms and signs is not limited when the infarct focus is confirmed by CT or MRI; (4). The symptoms and signs of the patients should last more than 24 hours when the responsible infarct was not found on CT or MRI; (5). Excluding stroke caused by other diseases; (6). Cerebral hemorrhage was excluded by CT or MRI.

2.4. Statistical analysis

Continuous variables are expressed as mean (standard deviation) and compared using the two-tailed *t*-test or the Mann-Whitney test. Categorical variables were compared using the 2 test or Fisher exact test. Univariate and multivariate logistic analyses were used to explore the risk factors for ischemic stroke. All patients were randomly divided into training and testing cohorts at a ratio of 7:3. The prediction ability of the five models was first evaluated by the ROC curve. All analysis was performed using the Python programming language (version 3.9.2, Python Software Foundation, https://www.python.org/) and R Project for Statistical Computing (version 4.0.4, http://www.r-project.org/). All *P* values were two-tailed, and $P < .05$ was considered statistically significant.

3. Results

3.1. Prevalence of patients with postoperative ischemic stroke

According to the inclusion criteria, 828 patients were enrolled. The characteristics and demographics of patients with hip or knee arthroplasty presenting with or without postoperative ischemic stroke were presented in Table 1. The prevalence of postoperative ischemic stroke was 6.16% (51/828) in the entire cohort initially received hip or knee arthroplasty. Overall, most patients with HCC presenting with postoperative ischemic stroke were male (52.9%), diabetes (62.7%), and higher American Society of Anesthesiologists (ASA) classification (74.5%). In terms of age, most patients with postoperative ischemic stroke were diagnosed at an older median age than those patients without postoperative ischemic stroke (63 vs 61 years, $P = .05$). No statistically significant difference was detected between the two cohorts concerning drinking status, smoking status, hypertension, or body mass index ($P = .23$–.87) except for the factors of neutrophil count, Lymphocyte count, low-density lipoprotein (LDL-C), total cholesterol, and serum creatinine ($P \leq .05$).

3.2. Risk Factors for predicting postoperative ischemic stroke

Risk factors associated with the development of postoperative ischemic stroke in patients with hip or knee arthroplasty were analyzed using univariate and multivariate logistic regression models, as presented in Table 2. Based on our results, age (OR: 1.31, 95%CI:0.85–2.01), ASA classification(II vs I: OR: 0.27, 95%CI: 0.03–2.34), diabetes (Yes vs No: OR: 5.69, 95%CI: 2.59–12.50), LDL-C (>3.6 vs ≤3.6: OR: 2.30, 95%CI: 1.10–4.81), Standard deviation of red blood cell distribution width (RDW-SD) (>13 vs ≤13: OR: 2.36, 95%CI: 1.15–4.85), and NLR(≥3.17 vs

Table 1

Baseline demographic and clinical characteristics of included patients diagnosed with or without ischemic stroke.

			Ischemic stroke		
Variables	**Level**	**Overall(N = 828)**	**Yes(N = 51)**	**No(N = 777)**	**P-value**
Age (median [IQR]),yr		61.00 [55.00, 70.00]	63.00 [59.00, 71.00]	61.00 [54.00, 70.00]	.05
Sex (%)	Female	190 (22.9)	24 (47.1)	166 (21.4)	.07
	Male	638 (77.1)	27 (52.9)	611 (78.6)	
ASA classification (%)	I	458 (55.3)	13 (25.5)	445 (57.3)	.02
	II	370 (44.7)	38 (74.5)	332 (42.7)	
Hypertension (%)	Yes	655 (79.1)	33 (64.7)	622 (80.1)	.37
	No	173 (20.9)	18 (35.3)	155 (19.9)	
Diabetes (%)	Yes	623 (75.2)	32 (62.7)	591 (76.1)	.02
	No	205 (24.8)	19 (37.3)	186 (23.9)	
Coronary disease (%)	Yes	185 (22.3)	4 (7.8)	181 (23.3)	.23
	No	643 (77.7)	47 (92.2)	596 (76.7)	
Smoking (%)	Yes	601 (72.6)	44 (86.3)	557 (71.7)	.28
	No	227 (27.4)	7 (13.7)	220 (28.3)	
Drinking (%)	Yes	653 (78.9)	36 (70.6)	617 (79.4)	.95
	No	175 (21.1)	15 (29.4)	160 (20.6)	
BMI (median [IQR]), Kg/m^2		26.00 [18.00, 31.00]	28.00 [21.00, 31.00]	26.00 [21.00, 29.00]	.87
SBP (median [IQR]),mm Hg		126.50 [109.00, 142.00]	119.00 [104.75, 129.50]	127.50 [109.00, 142.75]	.23
DBP (median [IQR]),mm Hg		83.00 [73.00, 92.00]	87.00 [73.00, 90.50]	83.00 [73.00, 92.00]	.96
RDW-SD (median [IQR])		16.50 [14.00, 18.75]	16.00 [13.00, 18.50]	16.00 [14.00, 18.00]	.43
RBC (median [IQR]),10^12/L		4.72 [2.12, 6.23]	4.12 [2.65, 5.63]	3.46 [2.14, 6.17]	.22
PLT (median [IQR]),10^9/L		200.00 [155.00, 260.50]	198.50 [158.25, 241.00]	200.00 [155.00, 263.50]	.64
NC (median [IQR]),%		4.16 [3.12, 6.46]	2.21 [1.23, 3.54]	4.23 [2.25, 5.65]	.01
LC (median [IQR]),%		2.08 [1.13, 3.23]	3.21 [2.75, 3.78]	1.56 [1.02, 3.18]	.01
LDL-C (median [IQR]),mmol/L		3.02 [2.04, 4.14]	3.23 [2.75, 3.25]	2.03 [1.54, 3.25]	.05
HDL-C (median [IQR]),mmol/L		3.25 [3.12, 5.35]	4.25 [3.21, 5.56]	3.25 [2.12, 4.75]	.33
TC (median [IQR]),mmol/L		5.25 [4.15, 6.25]	5.15 [4.15, 6.25]	4.12 2.55, 5.25]	.05
TG (median [IQR]),mmol/L		2.85 [1.24, 3.57]	2.26 [1.75, 3.45]	2.07 [1.21, 3.15]	.39
Scr (median [IQR]), Ïmol/L		121.00 [37.00, 146.00]	140.00 [35.50, 156.50]	82.00 [37.00, 146.00]	.12

ASA = American Society of Anesthesiologists, BMI = body mass index, DBP = diastolic pressure, HDL-C = high-density lipoprotein, IQR = Interquartile range, LC = Lymphocyte count, LDL-C = low-density lipoprotein, NC = Neutrophil count, PLT = blood platelet, RBC = red blood cell, RDW-SD = Standard deviation of red blood cell distribution width, SBP = systolic pressure, Scr = Serum creatinine, TC = total cholesterol, TG = triglyceride.

Table 2

Univariate and multivariate logistic regression analysis for risk factors associated with apoplexy in patients with hip or knee arthroplasty.

	Univerate		Multivariate#	
Variables	**OR(95%CI)**	**P-value**	**OR(95%CI)**	**P-value**
Age*	1.26 (0.86–1.83)	.02	1.31 (0.85–2.01)	.01
ASA				
II	Reference		Reference	
I	0.09 (0.01–0.64)		0.27 (0.03–2.34)	
Diabetes				
No	Reference		Reference	
Yes	19.79 (9.93–39.39)		5.69 (2.59–12.50)	
LDL-C				
>3.6	Reference		Reference	
=3.6	3.92 (2.04–7.53)		2.30 (1.10–4.81)	
RDW				
>13	Reference		Reference	
=13	3.79 (2.01–7.16)		2.36 (1.15–4.85)	
NLR				
	Reference		Reference	
=3.17	4.78 (3.84–5.72)		5.81 (4.86–6.75)	
LMR				
	Reference		Reference	
=3.6	2.51 (1.57–3.45)		2.24 (1.29–3.18)	.23
PLR				
	Reference		Reference	
=197	1.46 (0.52–2.40)		1.07 (0.12–2.01)	.21
Smoking				
No	Reference		Reference	
Yes	3.91 (2.97–4.85)		4.67 (3.73–5.61)	.07

* Continuous variable.
# Forward stepwise analysis.
ASA = American Society of Anesthesiologists.

<3.17: OR: 5.81, 95%CI: 4.86–6.75) were positively correlated with the development of postoperative ischemic stroke in patients with hip or knee arthroplasty at the initial diagnosis.

3.3. Selection and establishment of multiple models

A total of twenty-one preoperative variables were used to develop predictive models for postoperative ischemic stroke based on stepwise regression analysis. The intersection variable of all models was shown in Supplementary Digital Content Figures 1A, http://links.lww.com/MD2/B94. By feature selection, the candidate variables for each algorithm were ranked by their predictive importance, the meaningful variables are shown in Supplementary Digital Content Figures 1B, http://links.lww.com/MD2/B94. Consistent with the results of a generalized linear model, the top-ranked predictors were age, NLR, ASA classification, RDW, LDL-C, and diabetes.

3.4. Construction and validation of the nomogram

Considering the clinical utility, the top-ranked variables were identified to construct the optimal predictive model. The nomogram was constructed using the six significant factors listed above, which were generated from the multivariate analysis, to predict the risk of postoperative ischemic stroke in patients with hip or knee arthroplasty. The nomogram score was shown in Figure 2A. The weight of candidate variables was shown in Figure 2B. Furthermore, the decision curve showed the clinical values of these models were shown in Figure 2C. To verify the robustness of these models, the predictive performance of all models is shown in Figure 3A. The best performance was observed in model1(AUC: 0.90, 95%CI:0.85–0.95). The AUCs of the rest models were ranged from 0.82 (95%CI:0.77–0.86) to 0.85 (95%CI:0.81–0.91). Consistent with the ROC curves, the clinical impact curve showed that the risk of postoperative ischemic stroke could be readily distinguished in patients with hip or knee arthroplasty (Fig. 3B).

4. Discussion

Intra- or postoperative ischemic stroke after hip or knee arthroplasty has not been reported frequently to date, but it is one of the risk factors which is commonly identified during the consenting process for patients about to undergo surgery.[8–10] Previous studies demonstrated that older age, female gender, and white race were associated with a higher risk of developing a hip fracture among patients with ischemic stroke.[11–13] Consistent with previous studies, we found that the middle-aged and elderly cohort were associated with an increased risk of postoperative ischemic stroke after hip or knee arthroplasty. Indeed, patients with stroke are likely at greater risk for falls because of neurological impairments, such as leg weakness, sensory changes, visual, and balance issues.[14–16] Our study provided a real-world estimate of postoperative ischemic stroke in patients with hip or knee arthroplasty and suggested that the risk is even higher in patients with older age, lower NLR, higher ASA classification, higher RDW, higher LDL-C, and diabetes. To our knowledge, this is the first real-world study applying a generalized linear regression learning method for predicting postoperative ischemic stroke. We recommended that a deep learning signature-based nomogram could be used as a valuable tool for clinical decision-making.

In the present study, we identified several factors, including older age, lower NLR, higher ASA classification, higher RDW, higher LDL-C, and diabetes, correlated with greater odds of postoperative ischemic stroke at diagnosis. RDW is a cost-effective parameter associated with the incidence and prognosis of cerebrovascular diseases.[17] Consistent with our findings, patients with higher RDW were inclined to postoperative ischemic stroke. Previous studies have elucidated that inflammation

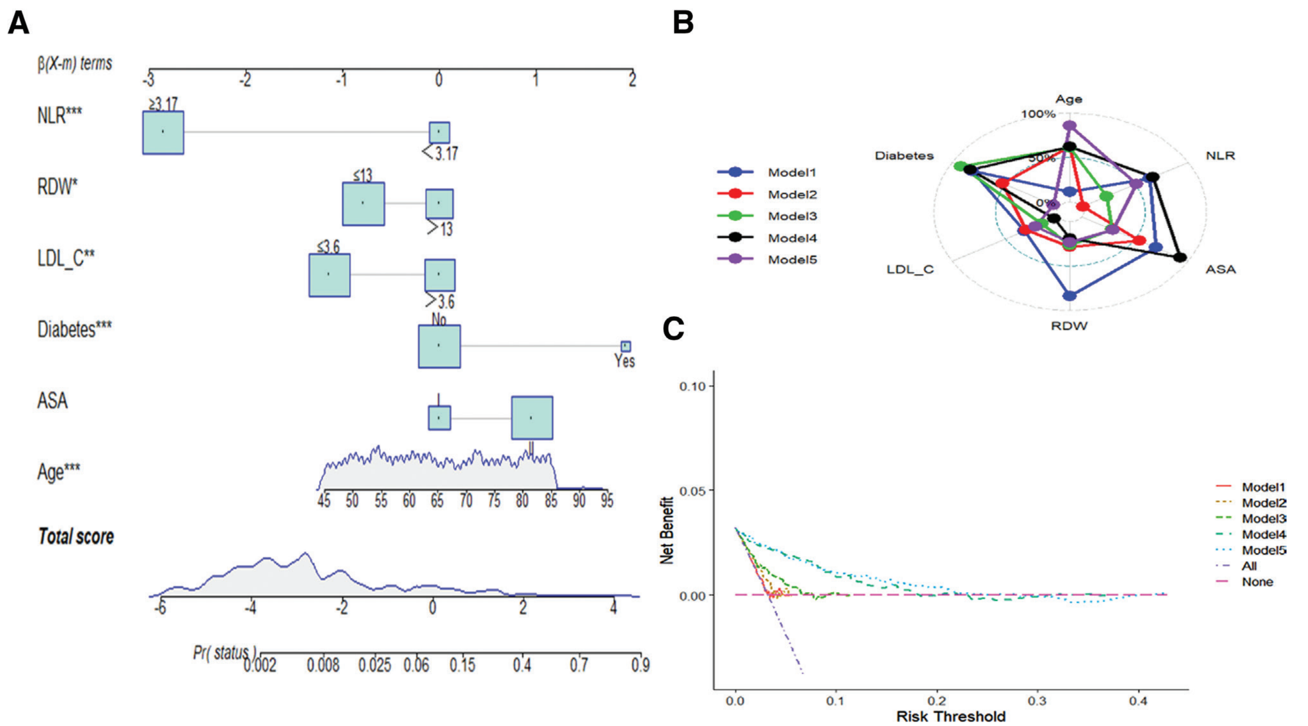

Figure 2. Nomogram to estimate the risk of ischemic stroke. (A) A nomogram for predicting the risk of ischemic stroke showing the proportion (%) of parameters included in the score scale. To use the nomogram score, it is important to identify the point of each variable on the corresponding axis; the total number of points can then be summated from all variables. (B) Radar plot showing the relative weight of candidate parameters arising from stepwise regression analysis. (C) Decision curve for the prediction of ischemic stroke. Decision curve analysis identified potential factors that can exert clinical influence based on stepwise regression analysis and the net benefit of using nomogram scores to stratify patients.

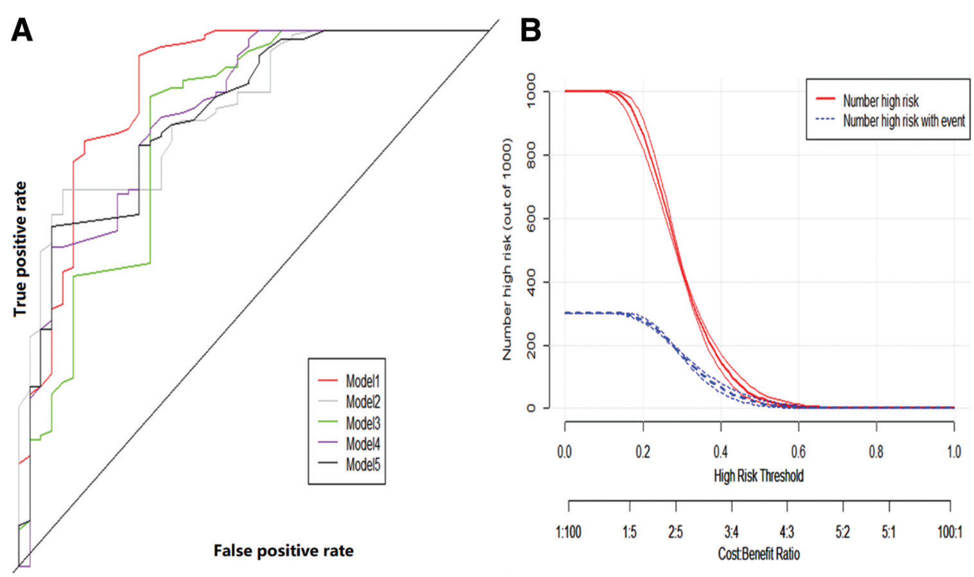

Figure 3. The predictive performance of different models. A. Receiver operating characteristic (ROC) curve for five models. B. Clinical impact curve for the ischemic stroke nomogram score. Notes. The purple line predicts the probability of patients who would show low risk to ischemic stroke. The red line calculated for predmodelB shows how many patients would be at a high risk of ischemic stroke.

is another important factor during ischemic stroke, which is consistent with our results.[18–21] Indeed, the inflammatory response plays an important role in tissue remodeling and repair during the recovery of nerve cells.[22] Therefore, understanding the effects of inflammation on the nervous system will provide a new direction for the prediction and treatment of postoperative ischemic stroke. Besides, age and sex also influenced ischemic stroke epidemiology, pathophysiology, and treatment efficacy.[23] It's not hard to understand that the aging process could lead to the emergence of characteristic phenotypes that include changes in body composition, energy production and utilization imbalance, homeostatic dysregulation, and neurodegeneration and loss of neuroplasticity.[24–26] In addition, we also revealed that higher LDL-C and diabetes will contribute to postoperative ischemic stroke in patients with hip or knee arthroplasty. Rao M.A et al reported that atherosclerosis (a risk factor for ischemic stroke) results from an accumulation of LDL-derived lipids in the arterial wall.[27] Consistent with previous studies, impaired fibrinolysis, as well as disordered lipid metabolism, have been recognized as risk factors for ischemic stroke.[28,29]

In our study, it is worth noting that diabetes was associated with a high risk of postoperative ischemic stroke. Previous studies have revealed that diabetes is a well-established risk factor for stroke, which can cause pathologic changes in blood vessels at various locations.[30,31] There are several possible mechanisms wherein diabetes leads to stroke, include vascular endothelial dysfunction, increased early-age arterial stiffness, systemic inflammation, and thickening of the capillary basal membrane.[30,32] Thus, our findings elucidate that NLR values can be reliably used to predict postoperative ischemic stroke. In addition, guidelines for the early management of patients with acute ischemic stroke were published in January 2018.[33] Consistent with the guidelines, we revealed that patients with higher ASA classification correlated with a high risk of postoperative ischemic stroke.

Our study should be considered in light of several limitations. First, our observations were limited to retrospective studies from a single-center, these findings need further multi-institutional validation with larger sample size. Second, our nomograms were merely validated via an internal training set, external verification using an independent patient set is necessary. Third, this is a retrospective study that could not completely avoid missing data and measurement biases, more candidate useful biomarkers may be needed to develop predictive models in the future.

5. Conclusion

We generated a risk scoring model incorporating several clinical and serological indicators. Based on ROC analysis and DCA evaluation, we recommended that older age, lower NLR, higher ASA classification, higher RDW, higher LDL-C, and diabetes were the most important predictive risk factors for postoperative ischemic stroke.

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Author contributions

Danfeng Dai and Zhichao Gao conceived the research. Danfeng Dai and Zhichao Gao analyzed the data and wrote the manuscript. All the authors were involved in the approval of the final version.
Conceptualization: Zhichao Gao.
Investigation: Sijia Tu.
Methodology: Danfeng Dai.
Software: Danfeng Dai, Sijia Tu.
Visualization: Danfeng Dai, Sijia Tu.
Writing – original draft: Danfeng Dai, Zhichao Gao, Sijia Tu.
Writing – review & editing: Zhichao Gao.

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