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A prediction model for the risk of gastrointestinal bleeding associated with antiplatelet therapy in patients with ischemic stroke

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Abstract

Objective: Patients with ischemic stroke (IS) undergoing antiplatelet therapy are at risk of gastrointestinal bleeding (GIB). This study aims to develop and validate a multivariable integrated risk prediction model for GIB, to optimize clinical decision-making. *Methods:* A retrospective cohort of IS patients who received antiplatelet therapy from 2020 to 2024 was included. Demographic characteristics and laboratory parameters (including complete blood count, coagulation profile, liver and kidney function tests, and stool occult blood) were collected. Predictive factors were selected using LASSO regression and logistic regression, and a nomogram model was constructed. Evaluation metrics included area under the curve (AUC), calibration curve (mean absolute error, MAE), and decision curve analysis (DCA). *Results:* Six independent risk factors were identified: C-reactive protein (CRP) ($p = 0.003$), hemoglobin (HGB) ($p < 0.001$), D-Dimer ($p = 0.039$), albumin/globulin ratio (ALB/GLB, $p = 0.021$), age ($p = 0.01$), and fibrinogen (FIB, $p = 0.037$), which collectively drive the risk of GIB. The predictive model demonstrated an AUC of 0.79 in both the training and validation cohorts, with MAE values ranging from 0.018 to 0.04, and a Hosmer-Lemeshow test result of $p > 0.05$. The model exhibited good fit, strong discrimination capability for GIB, and stable diagnostic performance. Decision curve analysis revealed significant net benefits within the risk threshold range of 0.2-1.
Conclusion: The developed nomogram model effectively predicts the risk of GIB in IS patients undergoing antiplatelet therapy, providing a basis for individualized treatment strategies.

Keywords: Ischemic stroke, gastrointestinal bleeding, antiplatelet therapy, risk prediction

INTRODUCTION

Stroke is the second leading cause of death and disability worldwide, with an especially prominent disease burden in China.[1] With the aging population and the rising prevalence of metabolic diseases, the incidence of stroke has been increasing year by year.[2] A large-sample study conducted in 2013, which included 480,687 cases, indicated that the age-standardized prevalence and incidence rates of stroke were 1114.8/100,000 person-years and 246.8/100,000 person-years, respectively.[3] More recent surveys show that between 2013 and 2019, the weighted prevalence of stroke significantly increased from 2.28% to 2.58%.[4] Ischemic stroke (IS), which accounts for approximately 70-80% of all strokes, is caused by cerebral artery occlusion leading to local brain tissue ischemia and hypoxic necrosis.[3,5,6]

Although antiplatelet therapy, as secondary prevention, significantly reduces the annual risk of recurrent vascular events and vascular mortality related to ischemic stroke, long-term treatment also increases the risk of bleeding complications, which may lead to severe disability or death.[7-9] The annual risk of major bleeding in patients with IS, transient ischemic attack (TIA), or myocardial infarction is 1.46%, with 40% of cases attributed to gastrointestinal bleeding (GIB).[10] Furthermore, the mortality risk for IS patients who experience GIB is increased by 10.98 times.[11] According to O'Donnell's report[12], the incidence of GIB during hospitalization for IS patients is 1.5%, with one-third of cases requiring blood transfusions. Another single-center study from Scotland[13] showed that the incidence of GIB in 613 IS patients over a 3-year period was 3%. Currently, clinical interventions for GIB mainly focus on post-event management, and there is a lack of effective early

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risk stratification tools. Although risk prediction models such as HAS-BLED, ATRIA, and ORBIT have been developed to assess the risk of GIB in patients undergoing thrombosis treatment and to guide treatment decisions[14], the best-performing HAS-BLED model has an AUC of only 0.68. Additionally, the sample sizes of these models are small (50-150 GIB events), and they do not incorporate newer antithrombotic/antiplatelet drugs, nor do they reflect the latest clinical advancements.[15,16]

Therefore, this study aims to construct and validate a nomogram prediction model specifically for GIB in patients with ischemic stroke undergoing antiplatelet therapy, helping clinicians to quickly identify high-risk IS patients for GIB and providing decision support for clinical practice.

METHODS

Study design

We conducted a retrospective analysis using electronic medical records from IS patients admitted by Tongde Hospital of Zhejiang Province, between January 2020 and December 2024. Inclusion criteria were: (1) Age ≥18 years; (2) Diagnosis of acute ischemic stroke within 7 days of onset[17]; (3) Standard antiplatelet therapy (aspirin and/or clopidogrel); (4) Complete clinical follow-up data. Exclusion criteria were: (1) Active gastrointestinal bleeding prior to admission or within 3 months; (2) Comorbid malignancies or other end-stage diseases; (3) Severe hepatic or renal dysfunction; (4) Post-thrombolysis or thrombectomy patients; (5) Chronic use of NSAIDs or corticosteroids; (6) Incomplete clinical data.

Data collection

Clinical data were collected from IS patients fllowing antiplatelet theorapy. Patients were stratified into GIB(+, ++, +++) and non-GIB(-) groups based on fecal occult blood test results. Collected parameters included: 1) Demographic characteristics: Age, sex; 2) Laboratory indicato: White Blood Cell Count(WBC#), Neutrophil Count(NEUT#), Neutrophil Percentage(NEUT%), Lymphocyte Count(LYM#), Lymphocyte Percentage(LYM%), Monocyte Count (MONO#), Monocyte Percentage(MONO%), Basophil Count(Baso#), Basophil Percentage(Baso%), Eosinophil Count(EOS#), Eosinophil Percentage(EOS%), Red Blood Cell Count(RBC#), Red Cell Distribution Width(RDW), hematocrit(HCT), Mean Corpuscular Volume (MCV), Hemoglobin (HGB), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration(MCHC), Platelet Count (PLT), Mean Platelet Volume(MPV), Platelet Distribution Width (PDW), Plateletcrit(PCT), Hemoglobin A1a(HbA1a), Hemoglobin A1b(HbA1b), Hemoglobin A1c(HbA1c), Glycated Hemoglobin(GHb), Aspartate Aminotransferase/ Alanine Aminotransferase Ratio(AST/ALT), β2-Microglobulin(β2-MG), D-3-Hydroxybutyric acid(D3H), Creatine Kinase-MB(CK-MB), C-reactive protein(CPR), Estimated Glomerular Filtration Rate(eGFR), Albumin(ALB), Albumin/ Globulin Ratio(ALB/GLB), Cholinesterase(ChE), Low Density Lipoprotein(LDL), Amylase(AMY), Glycyl Proline Dipeptidyl Aminopeptidase(GPDA), Triglyceride(TG), High-Density Lipoprotein(HDL), Gamma-Glutamyl Transferase(GGT), Alanine Aminotransferase(ALT), Aspartate Aminotransferase(AST), Creatinine(CREA), Myoglobin(MYO), High-sensitivity C-reactive protein(hs-CPR), Total Bilirubin(TBIL), Indirect Bilirubin(IBIL), Direct Bilirubin(DBIL), Alkaline Phosphatase (ALP), Creatine Kinase(CK), Urea, Uric Acid(UA), Glucose(GLU), hydroxybutyrate dehydrogenase(HBDH), Globulin(GLB), Lactate Dehydrogenase(LDH), Homocysteine(HCY), apolipoprotein E(ApoE), Alpha-L-fucosidase(AFU), Free Fatty Acid(FFA), Apolipoprotein A(ApoA), Apolipoprotein B(ApoB), Lipoprotein(a)(Lp(a)), Cholesterol(CHOL), Total Bile Acid(TBA), Total Protein(TP), Potassium(K), Phosphorus(P), Chloride(Cl), Sodium(Na), Magnesium(Mg), Total Calcium(Ca), D-Dimer(D-Dimer), Activated Partial Thromboplastin Time(APTT), International Normalized Ratio(PT-INR), Thrombin Time(TT), Prothrombin Time(PT), Fibrinogen(FIB).

Statistical analysis

All statistical analyses were performed using SPSS (version 25, IBM Corp, Armonk, NY, USA) and R software (version 3.5.3, R Core Team, Vienna, Austria). The $p < 0.05$ was considered statistically significant ($*p < 0.05$, $**p < 0.01$, $***p < 0.001$). For normally distributed continuous data, independent t-tests were used, with results presented as $\bar{x} \pm s$; for non-normally distributed data, the Kolmogorov-Smirnov non-parametric test was applied, and results were presented as

median (interquartile range) [M (IQR)]. Group comparisons for categorical variables were performed using the chi-square test, with results expressed as frequency (percentage) [n (%)].

Multiple imputation was used to fill in missing data, generating a complete dataset. The final dataset was randomly divided into a training set and a validation set in a 7:3 ratio. Feature selection was performed using LASSO regression, and a prediction model was constructed using logistic regression. Decision curve analysis (DCA) was conducted to assess clinical utility; calibration curve (mean absolute error, MAE) was drawn to examine the consistency between predicted and observed values; receiver operating characteristic (ROC) curves were analyzed to evaluate the discriminative ability of the model; the Hosmer-Lemeshow test was used to assess model goodness-of-fit ($p > 0.05$ indicates a good fit). The model's predictive accuracy was quantified using the area under the curve (AUC). Tolerance (TOL) and variance inflation factor (VIF) were used to detect multicollinearity among variables, with TOL ≤ 0.2 or VIF ≥ 5 indicating potential multicollinearity issues.

RESULTS

Baseline characteristics

This study included a total of 413 IS patients receiving antiplatelet therapy, with 94 patients in the GIB group and 319 patients in the non-GIB group. A comparative analysis of baseline data revealed significant differences between the two groups across multiple parameters ($p < 0.05$). Patients in the GIB group were significantly older than those in the non-GIB group (83 vs 71, $p < 0.001$). In terms of inflammatory markers, both NEUT# and NEUT% were significantly elevated, reaching up to 5.14×10^9/L($p = 0.002$) and 72.17%($p < 0.001$) respectively. In con1rast, the LYM% was decreased, with a minimum of 23.39%, $p = 0.038$. Additionally, EOS# and EOS% were higher ($p < 0.05$), indicating systemic inflammatory activation. Hematological parameters revealed significant reductions in red blood cell-related metrics (RBC#, HGB, HCT) ($p < 0.001$) and an increase in RDW ($p = 0.014$), suggesting anemia or hemodilution. Platelet metrics (PLT, PCT) and the SII also increased ($p < 0.05$), reflecting enhanced platelet activation and inflammatory-coagulation interaction. Liver function tests indicated abnormalities in the AST/ALT ($p = 0.001$), ALB ($p < 0.001$), and the ALB/GLB ($p < 0.001$), pointing to hepatocellular injury and impaired synthetic function. Additionally, renal function was assessed, with an elevated UREA level ($p = 0.035$) suggesting possible mild renal impairment. In terms of coagulation, significant elevations in D-Dimer ($p < 0.001$) and FIB ($p < 0.001$) were observed, along with prolonged APTT, PT-INR, and PT ($p \leq 0.001$). These findings collectively indicate a hypercoagulable state accompanied by increased fibrinolysis.

The abnormal changes in these parameters are interrelated, suggesting that systemic inflammatory responses may contribute to disease progression by activating the coagulation system and affecting liver, kidney, and hematopoietic functions. These findings provide critical laboratory evidence for clinical risk stratification and intervention strategies.

Variable selection

This study employed LASSO regression to identify predictors of GIB in IS patients. Results demonstrated that as the regularization parameter λ increased from logλ=-10 to -2, model complexity decreased accordingly. Cross-validation curves identified 11 key predictors: CK, CRP, HGB, APTT, D-Dimer, ALB/GLB, Age, FIB, AST/ALT, EOS%, and TT (Figure 1). VIF analysis confirmed no significant multicollinearity (all VIF ≤ 5), ensuring model stability. Subsequent multivariate logistic regression validated these predictors, identifying six statistically significant independent risk factors (Table 2): CRP ($p = 0.003$), HGB ($p < 0.001$), D-Dimer ($p = 0.039$), ALB/GLB ($p = 0.021$), Age ($p = 0.01$), and FIB ($p = 0.037$). These findings provide critical evidence for GIB risk assessment in ischemic stroke.

Prediction model construction

A nomogram for GIB risk prediction in IS patients was developed using LASSO-selected variables (Figure 2A). This model retained 11 predictors, enhancing sensitivity but increasing clinical complexity. To optimize practicality, a refined nomogram (Figure 2B) was constructed using six statistically significant ($p<0.05$) independent risk factors from multivariate logistic regression. This streamlined version improved clinical utility and interpretability by aligning variables with GIB pathophysiology. Reduced variables also minimized overfitting, enhancing model stability and generalizability.

Table 1: Baseline characteristics of IS

Items	Overall, N=413	No-GI Bleeding, N=319	GI Bleeding, N=94	Z/t/χ2	*p*
Hospital admission information,N					
Male	242(58.6%)	188(58.9%)	54(57.4%)	0.066	0.797
Female	171(41.4%)	131(41.1%)	40(42.6%)		
Age(y)	63(74,84)	71(62,81)	83(70.75,91)	-5.438	<0.001***
Blood Routine,IQR/mean±SD					
WBC#(10^9/L)	6.78±2.14	6.72±2.18	7.01±2	1.15	0.25
NEUT#(10^9/L)	3.28(4.5,6.1)	4.39(3.2,5.76)	5.14(3.68,7.23)	-3.162	0.002**
NEUT%(%)	67.77±11.68	66.48±11.24	72.17±12.12	4.24	<0.001***
LYM#(10^9/L)	1.25(1.6,2)	1.6(1.26,2.07)	1.5(1.2,1.81)	-1.66	0.097
LYM%(%)	25.27±9.95	25.81±9.85	23.39±10.12	-2.08	0.038*
MONO#(10^9/L)	0.3(0.47,0.6)	0.45(0.3,0.6)	0.5(0.34,0.61)	-1.507	0.132
MONO%(%)	5.6(6.9,8.6)	6.8(5.49,8.41)	7.15(5.76,8.9)	-1.731	0.083
Baso#(10^9/L)	0.02(0.03,0.05)	0.03(0.02,0.04)	0.03(0.02,0.05)	-1.333	0.183
Baso%(%)	0.3(0.49,0.7)	0.47(0.29,0.7)	0.5(0.3,0.7)	-0.58	0.562
EOS#(10^9/L)	0.08(0.16,0.28)	0.15(0.08,0.26)	0.2(0.11,0.3)	-2.487	0.013*
EOS%(%)	1.5(2.6,4.2)	2.5(1.41,3.94)	2.97(1.79,5.3)	-2.745	0.006**
RBC#(10^9/L)	3.94(4.27,4.56)	4.32(4,4.59)	3.98(3.65,4.37)	-5.055	<0.001***
RDW(%)	12.7(13.5,14.73)	13.4(12.7,14.58)	13.7(12.89,15.3)	-2.461	0.014
HCT(%)	36.1(38.6,41.18)	39.11(36.75,41.45)	36.76(32.55,40.07)	-4.87	<0.001***
MCV(fL)	88.9(91.6,94.7)	91.58(88.92,94.41)	91.7(87.97,95.33)	-0.184	0.854
HGB(g/L)	116.68(127.95,138.43)	130(119.36,139.92)	118.01(97.75,131.03)	-6.078	<0.001***
MCH(pg)	29.6(30.7,31.73)	30.7(29.65,31.69)	30.3(29.29,31.9)	-1.408	0.159
MCHC(g/L)	329.8(336,341)	336.2(330.1,341)	332.75(327.71,341)	-2.459	0.014*
PLT(10^9/L)	158(208.45,290)	202(154,279.97)	239(170.61,319.25)	-1.992	0.046*
MPV(fL)	9.04(9.9,10.9)	9.87(9,10.84)	9.9(9.3,11.1)	-1.244	0.213
PDW(%)	16(16,16.83)	16(16,16.87)	16(16,16.41)	-1.465	0.143
PCT(ng/mL)	0.16(0.21,0.29)	0.2(0.15,0.27)	0.24(0.18,0.31)	-2.522	0.012*
SII	549.48(785.45,1020)	811.43(582.28,1039.47)	674.78(500.41,935.97)	-2.175	0.03*
Glycometabolism, IQR/mean±SD					
HbA1a	1(1.1,1.28)	1.1(1,1.26)	1.1(0.96,1.3)	-0.904	0.366
HbA1b	0.8(1,1.31)	1(0.8,1.32)	0.9(0.8,1.33)	-0.316	0.752
HbA1c(%)	5.57(6.1,7)	6.1(5.51,7)	6.2(5.6,7.21)	-0.796	0.426
GHb(%)	7.55(8.3,9.4)	8.3(7.5,9.36)	8.24(7.7,9.6)	-0.487	0.626
GLU(mmol/L)	4.78(5.67,7.33)	5.67(4.58,7.32)	5.67(5.04,7.69)	-1.735	0.083
Liver Function, IQR/mean±SD					
ALT(u/L)	11.79(21,35.73)	21(11.94,36.12)	20.68(10.19,33.5)	-0.165	0.869
AST(u/L)	19(25.45,35.95)	26(19,35.78)	24.5(18,38)	-0.005	0.996
TBIL(umol/L)	0.93(1.43,2)	1.35(0.89,1.96)	1.69(1.15,2.28)	-3.221	0.001**
IBIL(umol/L)	9.1(13,18.2)	13.18(9.1,18.53)	12.25(9.03,17.65)	-0.952	0.341
DBIL(umol/L)	7.5(9.9,14.2)	10.2(7.52,14.45)	9.4(7.42,13.4)	-0.939	0.348
GGT(u/L)	1.86(2.7,3.8)	2.7(1.86,3.79)	2.7(1.88,3.95)	-0.269	0.788
ALT(u/L)	21(47,92.69)	51.04(22,97.23)	37.5(19.75,72.02)	-1.864	0.062
ALP(u/L)	53.13(76.4,99.14)	75.46(52.3,101.48)	78(60,96.75)	-1.026	0.305
TP(g/L)	63.9(67.2,70.45)	67.8(64.79,70.6)	64.92(61.15,69.71)	-3.456	0.001**
ALB(g/L)	38.59±4.13	39.16±3.96	36.64±4.11	-5.386	<0.001***
GLB(g/L)	26.1(28.5,31.5)	28.38(26.24,31.41)	28.82(25.78,31.61)	-0.342	0.732
ALB/GLB	1.36±0.29	1.39±0.29	1.26±0.27	-3.972	<0.001***
TBA(umol/L)	3.1(6.8,13.68)	7.41(3.33,14.56)	4.75(2.48,9.58)	-2.657	0.008**
ChE(u/L)	4376.45(6248,8274)	6278.87(3764.55,8329.9)	6157.34(5182.75,7672.75)	-0.382	0.702

Renal Function, IQR/mean±SD					
CREA(umol/L)	55.68(75.4,105.41)	75.93(55,110.08)	75.01(58.19,99.33)	-0.121	0.903
Urea(mmol/L)	4.64(6.2,8.4)	6.1(4.62,7.95)	6.75(5.08,9.23)	-2.105	0.035*
UA(umol/L)	340.11±139.47	341.34±139.57	335.93±139.77	-0.33	0.741
Egfr(ml/min)	64.35(83.7,97)	84(65.74,97.43)	80.5(58,95.04)	-1.651	0.099
Myocardial Enzymes, IQR/mean±SD					
CK(u/L)	46.8(87,141.29)	94.97(50.14,144.76)	66.75(34.18,109.48)	-3.037	0.002**
CK-MB(ng/mL)	1.93(2.77,3.96)	2.73(1.93,3.95)	2.95(2.01,4.03)	-0.801	0.423
HBDH(u/L)	91.3(112,141)	112(90.03,137.54)	110.5(94.75,152.08)	-1.214	0.225
LDH(u/L)	165(197.74,241)	201(165.79,240)	191.5(157.75,244.25)	-0.039	0.969
MTO(ng/L)	22.89(40.3,75.13)	39.6(22.5,75.27)	43.54(23.85,74.08)	-0.313	0.754
Blood Fat, IQR/mean±SD					
TG(mmol/L)	0.89(1.41,1.96)	1.39(0.89,1.97)	1.44(0.91,1.95)	-0.347	0.729
CHOL(mmol/L)	3.11(3.74,4.54)	3.74(3.11,4.51)	3.82(3.1,4.71)	-0.115	0.909
HDL(mmol/L)	0.91(1.13,1.36)	1.15(0.92,1.39)	1.06(0.87,1.34)	-1.093	0.274
LDL(mmol/L)	1.75(2.21,2.81)	2.21(1.74,2.79)	2.17(1.81,2.92)	-0.533	0.594
ApoA(g/L)	1.06(1.26,1.51)	1.26(1.07,1.52)	1.22(1.04,1.49)	-0.615	0.539
ApoB(g/L)	0.6(0.78,0.98)	0.75(0.57,0.98)	0.83(0.69,0.99)	-2.021	0.043*
ApoE(mg/L)	20.58(29.9,40.1)	30.1(20.5,41.01)	28.98(20.45,37.29)	-0.742	0.458
FFA(mmol/L)	112(273,522)	274.96(118.02,550.07)	269.5(103.24,460.84)	-0.141	0.888
Lp(a)(mg/L)	0.35(0.66,1.17)	0.66(0.34,1.1)	0.68(0.44,1.3)	-1.298	0.194
Coagulation Function, IQR/mean±SD					
D-Dimer(ug/Ml)	0.39(1.09,2.33)	0.92(0.36,2.11)	1.45(0.67,4.24)	-4.059	<0.001***
APTT(s)	26.1(27.9,30.8)	27.52(25.7,30.43)	29(26.88,32.83)	-3.414	0.001**
PT-INR	0.99(1.05,1.12)	1.04(0.98,1.1)	1.09(1.01,1.2)	-4.359	<0.001***
TT(s)	16.16(17.1,18)	17.1(16.02,17.9)	17.2(16.4,18.26)	-1.852	0.064
PT(s)	10.9(11.5,12.34)	11.4(10.8,12.12)	12.1(11.18,13.1)	-4.419	<0.001***
FIB(g/L)	2.64(3.3,4.21)	3.15(2.55,4.04)	3.87(3.03,5.21)	-4.683	<0.001***
Electrolyte, IQR/mean±SD					
K(mmol/L)	4.06±0.62	4.01±0.59	4.21±0.71	2.672	0.008**
P(mmol/L)	1.04(1.18,1.32)	1.19(1.01,1.34)	1.16(1.06,1.29)	-0.649	0.516
Cl(mmol/L)	101.75(104.83,107.2)	104.8(101.99,107.07)	105.15(99.68,107.78)	-0.165	0.869
Na(mmol/L)	138.1(140.7,142.8)	140.71(137.93,142.82)	140.6(138.47,142.72)	-0.229	0.819
Mg(mmol/L)	0.87±0.14	0.87±0.14	0.87±0.14	-0.136	0.892
Ca(mmol/L)	2.14(2.24,2.38)	2.24(2.14,2.38)	2.24(2.16,2.37)	-0.476	0.634
Other Indicators, IQR/mean±SD					
β2-MG(mg/L)	1.67(2.68,4.16)	2.48(1.55,3.98)	3.04(2.06,5.03)	-3.017	0.003**
D3H(mmol/L)	0.16(0.72,1.49)	0.76(0.19,1.47)	0.69(0.06,1.52)	-1.143	0.253
CPR(mg/L)	3.41(13.27,34.65)	14.66(3.83,35.38)	8.03(2.65,29.81)	-1.59	0.112
AMY(u/L)	37.34(59.13,84)	59(35.31,84.37)	62(46.27,84.27)	-1.464	0.143
GPDA(u/L)	25.73(39,54.78)	40(24.8,55.5)	38(28.75,52)	-0.51	0.61
hs-CPR(mg/L)	2.3(9.5,30.5)	8.64(1.6,26.86)	15.72(5.6,45.53)	-3.375	0.001**
HCY(umol/L)	7.71(12,15.78)	11.87(7.28,15.56)	13.03(9.18,17.03)	-2.246	0.025*
AFU(u/L)	14.78(21,28)	20.66(14,28.27)	22(16,28.25)	-1.152	0.249

$t/\chi^2/Z$: Student t-test; Pearson's Chi-squared test; Kolmogorov-Smirnov test. IQR: interquartile range, SD: standard deviation,
* The difference is statistically significant(*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

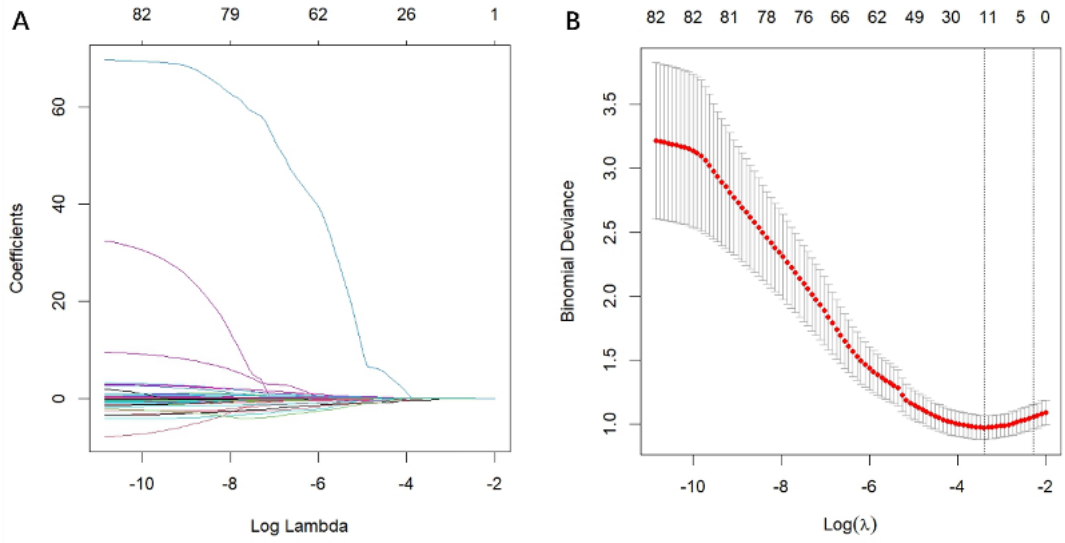

Figure 1. Cross validation of LASSO regression.

Diagnostic performance

The LASSO-based Prediction model (Figure 3) demonstrated strong discriminative ability in the training set (AUC = 0.82, 95% CI: 0.76-0.87), with consistent performance in the validation set (AUC = 0.79, 95% CI: 0.68-0.90), confirming robust generalizability. Hosmer-Lemeshow tests (training $p = 0.362$, validation $p = 0.512$) and calibration curves (training MAE = 0.034, validation MAE = 0.044) indicated excellent model fit and accurate risk prediction. DCA revealed significant clinical net benefit at high-risk thresholds, supporting its utility in balancing antiplatelet therapy and GIB risk.

The refined logistic regression-based nomogram (Figure 4) maintained comparable discrimination (training AUC = 0.79, validation AUC = 0.79) and model fit (Hosmer-Lemeshow $p = 0.275$ and $p = 0.513$) while improving calibration (training MAE = 0.018, validation MAE = 0.04). Its decision curve showed superior net benefit in the 0.2-1 threshold range. Comparative analysis confirmed that both models achieved AUC ≥ 0.8 with stable validation performance, yet the logistic model, with fewer variables enhanced predictive accuracy—particularly in calibration and clinical utility at key thresholds. This validated variable selection efficiency and suggested better generalizability and clinical applicability, offering an optimized solution for GIB risk stratification in ischemic stroke.

Table 2: Multivariate logistic regression and collinearity analysis

Items	B	standard error	Z value	Pr(>|z|)	Tolerance	VIF
CK	-0.004	0.002	-1.804	0.071	0.860	1.163
CPR	-0.020	0.007	-2.989	0.003 **	0.862	1.159
HGB	-0.030	0.008	-3.543	<0.001 ***	0.798	1.253
APTT	0.058	0.035	1.671	0.095	0.836	1.196
D-Dimer	0.112	0.054	2.059	0.039 *	0.770	1.299
ALB/GLB	-1.175	0.509	-2.308	0.021 *	0.938	1.066
Age	0.028	0.011	2.560	0.01 *	0.898	1.114
FIB	0.235	0.113	2.089	0.037 *	0.740	1.352
AST/ALT	0.298	0.163	1.831	0.067	0.880	1.137
EOS%	0.095	0.061	1.557	0.120	0.927	1.079
TT	0.085	0.089	0.953	0.341	0.871	1.148

* The difference is statistically significant(*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

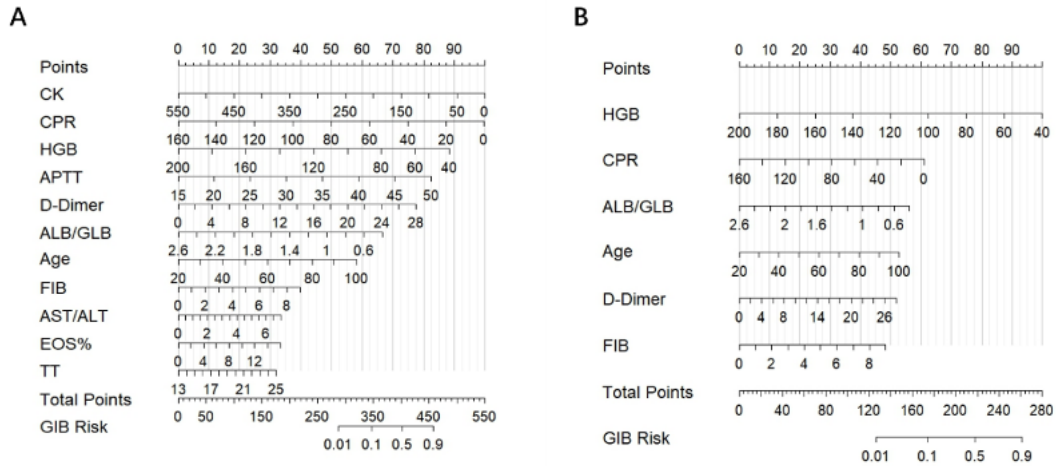

Figure 2. (A) Nomogram established based on LASSO regression; (B) Nomogram based on logistic regression.

DISCUSSION

This study developed and validated a GIB risk prediction model for IS patients receiving antiplatelet therapy. To preserve clinical utility, six key predictors were identified: CRP ($p = 0.003$), HGB ($p < 0.001$), D-Dimer ($p = 0.039$), ALB/GLB ($p = 0.021$), Age ($p = 0.01$), and FIB ($p = 0.037$). These parameters are readily obtainable upon admission, enabling rapid clinical assessment. The model demonstrated strong discriminative ability (AUC = 0.79) and calibration (MAE = 0.018-0.04) in both training and validation sets, providing clinicians with a reliable risk stratification tool.

The mechanisms underlying GIB in IS are complex, with antiplatelet use, stress, vagal hyperactivity, and noradrenergic activation

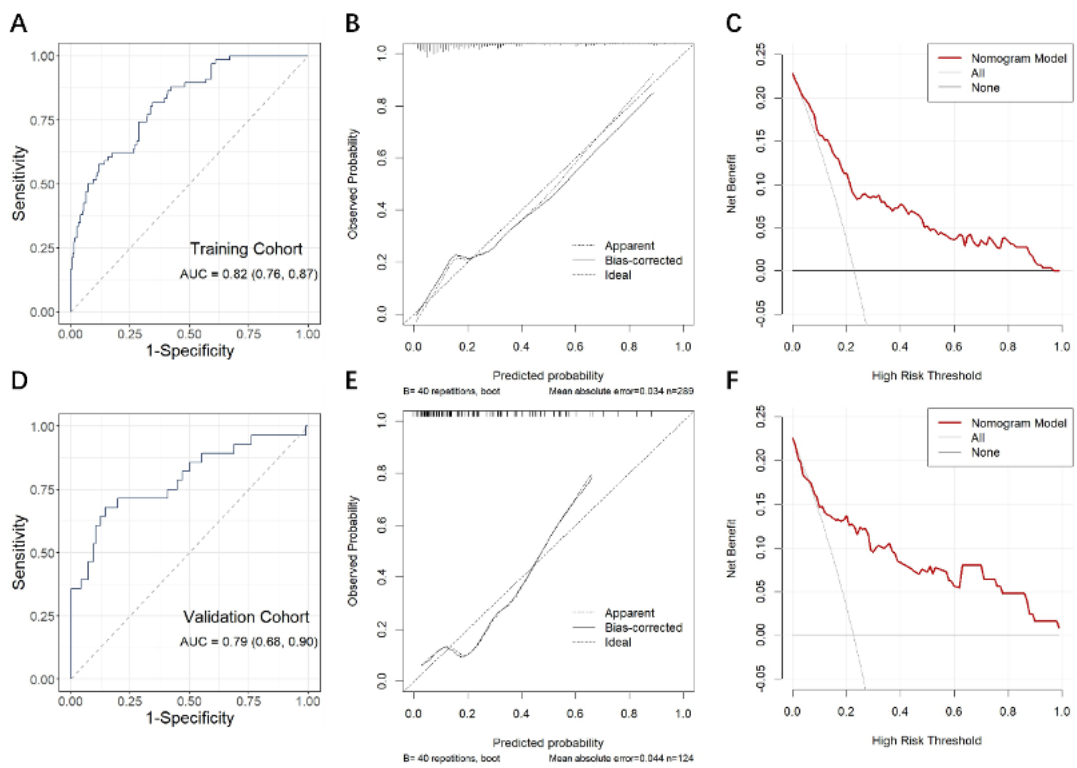

Figure 3. (A~C) AUC, MAE, and DCA of the training set based on LASSO regression; (D~F): AUC, calibration curve, and DCA of the validation set.

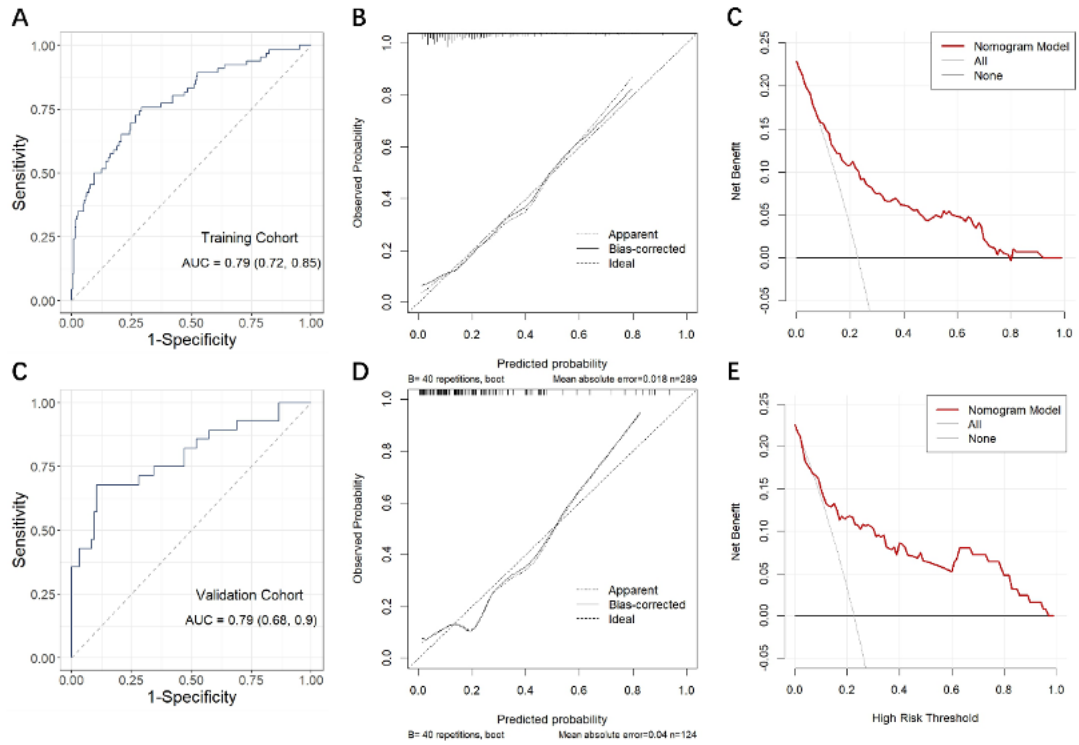

Figure 4. (A~C) AUC, calibration curve, and DCA of the training set based on logistic regression; (D~F): AUC, calibration curve, and DCA of the validation set.

recognized as key contributors to post-IS mucosal injury.[18] Consistent with prior studies[19,20], advanced age emerged as a significant risk factor, mediated through multiple pathophysiological pathways. First, age-related mucosal defense impairment, NSAID-induced prostaglandin suppression, and gastric hypermotility promote microvascular dysfunction and neutrophil activation, increasing mucosal injury risk.[21,22] Second, reduced PDGF-B synthesis compromises angiogenesis.[23] Finally, age-related pharmacokinetic changes and polypharmacy further complicate treatment.[24] These factors collectively elevate GIB risk in elderly patients. Peptic ulcers (33.1%) and gastroduodenal erosions (28.5%) represent the predominant GIB etiologies in IS patients.[25] Elevated CRP levels (28.7 mg/L in GIB vs 9.3 mg/L in non-GIB) suggest systemic inflammation contributes to GIB pathogenesis. Hemoglobin dynamics provide direct evidence of bleeding[26], while coagulation-fibrinolysis markers offer critical insights: Elevated D-Dimer (2.8 vs 0.6 μg/mL) indicates secondary hyperfibrinolysis and coagulation factor consumption.[27] Reduced ALB/GLB reflects impaired hepatic synthetic function, while paradoxically, high FIB (> 4 g/L) increases GIB risk by promoting microthrombosis-induced mucosal ischemia. It may be attributed that ischemic endothelial damage triggers t-PA release, further activating fibrinolysis (D-Dimer↑).[28] These interconnected biomarkers establish a predictive framework for early GIB risk identification in IS patients.

Existing evidence[29,30] confirms that GIB in IS patients significantly correlates with increased 1-year mortality, prolonged hospitalization, and higher disability rates. Compared to established prediction tools like PRECISE-DAPT (AUC = 0.66-0.72)[31,32] and CRUSADE (AUC = 0.62-0.77)[33,34], our model demonstrates superior discriminative performance (AUC = 0.79-0.82). Its innovative incorporation of ALB/GLB ratio and D-Dimer elucidates the inflammation-coagulation interplay, enhancing predictive accuracy. Clinically, unlike S2TOP-BLEED requiring specialized tests[35], our model exclusively utilizes routine admission parameters, optimizing emergency utility. This retrospective study may incur selection bias. Unaccounted confounders like proton pump inhibitor use and lack of external validation warrant caution in interpretation. Future multicenter prospective studies should validate these findings and develop dynamic models incorporating therapeutic responsiveness.

In conclusion, we developed and validated a GIB risk prediction model for antiplatelet-treated IS patients using six routinely available indicators (CRP, HGB, D-Dimer, ALB/GLB, Age, FIB). Despite retrospective design limitations, this tool supports personalized antiplatelet decision-making.

DISCLOSURE

Data availability: The raw data supporting the conclusions of this article is available upon request to the authors.

Ethics: The studies were approved by the Ethics Committee of Tongde Hospital of Zhejiang Province, Ethics Number: 2025-248(K).

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Conflict of interest: None

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