Am J Transl Res 2025;17(7):5011-5024
www.ajtr.org /ISSN:1943-8141/AJTR0164972

Original Article

Risk factors and predictive model for gastrointestinal bleeding in patients with ischemic stroke: a case-control study

Kaijun Feng, Qiuming Song, Ming Xue

Department of Critical Care Medicine, The Third People's Hospital of Hefei (Hefei Third Clinical College of Anhui Medical University), Hefei 230022, Anhui, China

Received April 1, 2025; Accepted June 11, 2025; Epub July 15, 2025; Published July 30, 2025

Abstract: Objective: To identify risk factors for gastrointestinal bleeding (GIB) in patients with ischemic stroke and to develop a clinically applicable predictive model. Methods: A retrospective case-control study was conducted on ischemic stroke patients admitted to The Third People's Hospital of Hefei. The training cohort included 96 patients who developed GIB between January 2021 and January 2023 (as cases) and 104 age-matched stroke patients who did not develop GIB (as controls). Risk factors were identified using univariate and multivariate logistic regression analyses. A separate validation cohort (40 GIB-cases and 48 controls) admitted between February 2023 and June 2024 was used to assess model's performance. Results: Univariate analysis identified several significant risk factors, including a history of gastrointestinal diseases, use of anticoagulants or antiplatelet drugs, a Glasgow Coma Scale (GCS) score ≤ 8, and prolonged prothrombin time (PT). Multivariate analysis showed that all four factors were independent predictors: history of stomach or intestinal disease (odds ratio [OR]=3.31, 95% confidence interval [CI]: 1.04-10.49), use of anticoagulants or antiplatelet drugs (OR=4.09, 95% CI: 1.68-9.99), GCS score ≤8 (OR=4.75, 95% CI: 1.18-19.16), and prolonged PT (OR=1.15, 95% CI: 1.04-1.28). A predictive nomogram based on these four factors demonstrated good performance, with an area under the curve (AUC) of 0.73 in the training cohort and 0.79 in the validation cohort. The calibration curve indicated that the nomogram's predictions matched closely with real outcomes. The decision curve analysis (DCA) also showed that the model provided evident clinical benefits. Conclusion: Four independent risk factors for GIB in ischemic stroke patients were identified. The developed nomogram may assist clinicians in early risk assessment and inform treatment decisions.

Keywords: Ischemic stroke, gastrointestinal bleeding, case-control study, risk factors, predictive model

Introduction

Ischemic stroke is one of the most common types of cerebrovascular disease worldwide. It is marked by a significant nerve function impairment, leading to high incidence of disability or death, especially in patients with severe conditions [1, 2]. According to the Global Burden of Disease (GBD) study, about 7 million people are newly diagnosed with ischemic stroke each year, making up over 70% of all stroke cases globally [3]. In addition to its efect on the nervous system, ischemic stroke can affect other body systems, with gastrointestinal bleeding (GIB) being one of the more common complications [4]. The incidence of GIB in ischemic stroke patients ranges from 1.5% to 8.0%, depending on the patient population and their clinical situations [5]. GIB can exacerbate brain damage by reducing cerebral blood flow, increasing the risk of recurrent strokes, and worsening overall outcomes [6].

The etiology of GIB in stroke patients is multifactorial, with several concurrent factors contributing to its development [7]. Research suggests that pre-existing comorbidities, coagulation abnormalities, the use of anticoagulants or antiplatelet drugs, and damage to the gastrointestinal mucosa may all contribute to GIB [8, 9]. However, many studies have not developed comprehensive models to accurately identify high-risk individuals for GIB [10]. Some studies focus mainly on the effects of anticoagulants or

antiplatelet drugs on bleeding, neglecting other possible risk factors, such as coagulation profiles or the extent of brain injury [11]. At present, there is still no consensus on the specific risk factors for GIB in ischemic stroke patients, and tools for predicting bleeding risk remain limited. Existing scoring systems, such as HAS-BLED and CHA_2DS_2-VASc, are primarily designed to evaluate anticoagulation-associated bleeding risks rather than ischemic stroke itself, limiting their clinical applicability [12, 13].

In our clinical practice, we have observed numerous ischemic stroke patients who subsequently developed significant GIB, often with adverse effects on clinical outcomes and long-term prognosis. However, the clinical factors associated with increased bleeding risk in this population remain poorly defined. To address this gap, we conducted a retrospective case-control study, collecting data on comorbidities, coagulation values, and antithrombotic treatment in ischemic stroke patients who developed GIB, and compared these findings with age - matched controls without GIB. Based on these findings, we developed a visualized nomogram model to facilitate individualized risk prediction. This study aims to identify the clinical factors associated with GIB in ischemic stroke patients and provide a practical tool for early risk identification and targeted preventive strategies to improve outcomes.

Patients and methods

Study design

This retrospective, single-center case-control study reviewed the clinical data of inpatients diagnosed with ischemic stroke at the Third People's Hospital of Hefei (Hefei Third Clinical College of Anhui Medical University). Patients were grouped based on their admission period: 200 patients in the training group (from January 2021 to January 2023) and 88 patients in the validation group (from February 2023 to June 2024). All data were retrieved from the hospital's electronic medical records system and were carefully checked by trained personnel to ensure completeness and accuracy. The study was approved by the hospital's ethics committee.

To determine the appropriate sample size, calculations were based on the estimated incidence of GIB in ischemic stroke patients and the expected difference between study groups. Assuming an odds ratio (OR) of 2.5 for a key risk factor, a statistical power of 80%, a two-tailed alpha of 0.05, and a roughly 1:1 case-to-control ratio, the required sample size was at least 90 patients per group. Ultimately, a total of 288 patients were included, exceeding this minimum requirement. Following standard protocols for prognostic modeling research, participants were assigned to the training and validation cohorts in a 2:1 ratio [14]. The larger training cohort was used for model development, while the smaller validation cohort was used for internal performance evaluation. This 2:1 division was designed to optimize model stability while preserving an independent set of cases for validation.

Definition of cases and controls

Patients in the case group encompassed those diagnosed with ischemic stroke, who received antithrombotic therapy upon admission and subsequently developed GIB during hospitalization. GIB was diagnosed based on clinical manifestations (e.g., hematemesis, melena, hematochezia) and confirmed by endoscopic or imaging evaluation. To ensure consistency, all cases had a stroke onset-to-admission time of ≤72 h. In total, 136 patients were included in the case group, comprising 96 in the training cohort and 40 in the validation cohort.

For each case, at least one age-matched control patient (±2 years) was selected from hospitalized ischemic stroke patients who did not develop GIB during their hospital stay. Control patients received a similar antithrombotic treatment regimen as the cases. A total of 152 control patients were included, with 104 in the training cohort and 48 in the validation cohort.

Exclusion criteria included patients under 18 years of age, those with severe cardiac, neurological, pulmonary, or renal dysfunction, individuals with a hospital stay of less than 8 h, those diagnosed with hematologic or immune system disorders, and patients with a history of psychiatric illness.

Data collection

A comprehensive dataset was collected by trained clinicians, including demographic char-

Table 1. Comparison of clinical characteristics between the training and validation cohorts

	Training cohort ($\bar{x}\pm s$)/n (%)/M (P25, P75)	Validation cohort ($\bar{x}\pm s$)/n (%)/M (P25, P75)	$t/\chi^2/Z$	*P*
Participants	200	88		
Age	68.44±12.05	70.53±10.74	1.403	0.162
Gender			0.367	0.545
Female	71 (35.50)	28 (31.82)		
Male	129 (64.50)	60 (68.18)		
BMI (kg/m^2)	22.58±2.58	22.32±1.98	0.917	0.360
Educational level			1.316	0.518
Primary school	66 (33.00)	27 (30.68)		
Middle and high school	100 (50.00)	41 (46.59)		
College	34 (17.00)	20 (22.73)		
GCS score			0.158	0.984
15	85 (42.50)	37 (42.05)		
13-14	62 (31.00)	26 (29.55)		
9-12	35 (17.50)	17 (19.32)		
3-8	18 (9.00)	8 (9.09)		
NIHSS score			0.611	0.894
0-1	105 (52.50)	45 (51.14)		
2-4	39 (19.50)	17 (19.32)		
5-15	41 (20.50)	17 (19.32)		
16-42	15 (7.50)	9 (10.23)		
History of stroke			0.126	0.723
No	153 (76.50)	69 (78.41)		
Yes	47 (23.50)	19 (21.59)		
History of gastrointestinal disease			0.408	0.523
No	178 (89.00)	76 (86.36)		
Yes	22 (11.00)	12 (13.64)		
Brain herniation			0.089	0.765
No	196 (98.00)	86 (97.73)		
Yes	4 (2.00)	2 (2.27)		
Cardiac failure			0.003	0.955
No	186 (93.00)	82 (93.18)		
Yes	14 (7.00)	6 (6.82)		
Renal dysfunction			0.027	0.870
No	183 (91.50)	80 (90.91)		
Yes	17 (8.50)	8 (9.09)		
Hepatic cirrhosis			0.042	0.838
No	185 (92.50)	82 (93.18)		
Yes	15 (7.50)	6 (6.82)		
Hypertension			0.087	0.768
No	51 (25.50)	21 (23.86)		
Yes	149 (74.50)	67 (76.14)		
Diabetes			0.013	0.909
No	149 (74.50)	65 (73.86)		
Yes	51 (25.50)	23 (26.14)		
Atrial fibrillation			0.134	0.714
No	179 (89.50)	80 (90.91)		
Yes	21 (10.50)	8 (9.09)		
Use of anticoagulants or antiplatelet agents			0.009	0.925
No	35 (17.50)	15 (17.05)		
Yes	165 (82.50)	73 (82.95)		

PTA (%)	94.41 (86.43, 101.17)	93.95 (84.84, 102.92)	0.474	0.636
PT (s)	11.89 (9.61, 13.81)	10.59 (9.15, 13.94)	0.902	0.367
APTT (s)	26.52 (24.88, 28.53)	26.38 (24.43, 28.46)	1.112	0.266
FBG (g/L)	2.76 (2.48, 3.15)	2.85 (2.49, 3.12)	0.316	0.752
ALP (IU/L)	85.78 (77.26, 96.27)	86.53 (76.32, 93.64)	0.592	0.554
UA (μmol/L)	339.72 (299.83, 386.75)	337.32 (313.55, 362.42)	0.523	0.601
Cr (μmol/L)	83.40 (75.88, 93.98)	82.65 (80.49, 87.15)	0.230	0.818
LDL (mmol/L)	2.42 (1.63, 3.20)	2.46 (2.12, 2.90)	0.458	0.647
HDL (mmol/L)	1.08 (0.99, 1.18)	1.10 (1.03, 1.15)	0.070	0.944
TG (mmol/L)	1.25 (0.79, 1.57)	1.25 (1.09, 1.36)	0.414	0.679
Hcy (μmol/L)	15.37 (9.63, 20.65)	16.70 (11.79, 22.01)	1.377	0.169

BMI: body mass index; GCS: Glasgow Coma Scale; NIHSS: National Institutes of Health Stroke Scale; PTA: prothrombin activity; PT: prothrombin time; APTT: activated partial thromboplastin time; FBG: fibrinogen; ALP: alkaline phosphatase; UA: uric acid; Cr: creatinine; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglycerides; Hcy: homocysteine.

acteristics (age, gender, BMI, educational level), neurological assessment scores (Glasgow Coma Scale [GCS] and National Institutes of Health Stroke Scale [NIHSS], both assessed at admission), and medical history (e.g., history of stroke, history of gastrointestinal disease). Data on comorbid conditions (e.g., brain herniation, cardiac failure, renal dysfunction, hepatic cirrhosis, hypertension, diabetes, atrial fibrillation) and antithrombotic medication use (anticoagulants or antiplatelet agents) were also recorded. Laboratoryvalues, including coagulation profiles, blood lipid levels, uric acid, creatinine, and homocysteine, were extracted from the first blood test performed upon hospital admission. In the case group, medication records reflected prescriptions prior to the first GIB episode.

Statistical methods

All statistical analyses were conducted using SPSS 22.0. The Kolmogorov-Smirnov test was performed to assess the normality of data distribution. For normally distributed continuous variables, Student's t-test was used for group comparisons, whereas the Mann-Whitney U test was applied for non-normally distributed continuous variables. Categorical variables were expressed as n (%) and analyzed using the χ^2 test. A *P*-value <0.05 was considered significant.

Univariate logistic regression analysis was first conducted to identify potential risk factors, and multivariate logistic regression analysis was subsequently performed to determine independent risk factors. Based on these findings, a nomogram prediction model was developed. The model's predictive performance and clinical utility were validated using calibration curves, receiver operating characteristic (ROC) curve analysis, and decision curve analysis (DCA).

Results

Clinical characteristics of the training and validation cohorts

As shown in **Table 1**, there were no significant differences between the two cohorts in terms of baseline demographics (age, gender, BMI, educational level), clinical severity scores (GCS score, NIHSS score), history of stroke, major comorbidities (e.g., hypertension, diabetes, and other comorbidities), use of antithrombotic therapy, or laboratory values (*P*>0.05).

Clinical characteristics of the case and control groups in the training cohort

Within the training cohort (**Table 2**), a GCS score of 3-8 was markedly more common among the case group (15.63%) compared to the control group (2.89%) (*P*=0.004). The proportion of patients with a history of gastrointestinal disease was higher in the case group (17.71% vs. 4.81%, *P*=0.004). The use of anticoagulants or antiplatelet agents was significantly more prevalent in the case group (91.67% vs. 74.04%, *P*=0.001). The median prothrombin time (PT) was longer in the case group [12.29 (10.23, 14.19) s] than in controls [10.96 (8.79, 13.02) s] (*P*=0.006). No significant differences were noted between cases and controls for age, gender, BMI, educational level, NIHSS score, history of stroke, comorbidi-

Table 2. Comparison of clinical characteristics between case and control groups in the training cohort

	Case group ($\bar{x}\pm s$)/n (%)/M (P25, P75)	Control group ($\bar{x}\pm s$)/n (%)/M (P25, P75)	$t/\chi^2/Z$	*P*
Participant	96	104		
Age	68.94±12.33	67.98±11.83	0.560	0.576
Gender			0.379	0.538
Female	32 (33.33)	39 (37.50)		
Male	64 (66.67)	65 (62.50)		
BMI (kg/m^2)	22.68±2.74	22.49±2.45	0.492	0.623
Educational level			0.572	0.751
Primary school	34 (35.42)	32 (30.77)		
Middle and high school	47 (48.96)	53 (50.96)		
College	15 (15.63)	19 (18.27)		
GCS score			13.243	0.004
15	33 (34.38)	52 (50.00)		
13-14	28 (29.17)	34 (32.69)		
9-12	20 (20.83)	15 (14.42)		
3-8	15 (15.63)	3 (2.89)		
NIHSS score			2.870	0.412
0-1	50 (52.08)	55 (52.88)		
2-4	16 (16.67)	23 (22.12)		
5-15	20 (20.83)	21 (20.19)		
16-42	10 (10.42)	5 (4.81)		
History of stroke			0.663	0.415
No	71 (73.96)	82 (78.85)		
Yes	25 (26.04)	22 (21.15)		
History of gastrointestinal disease			8.486	0.004
No	79 (82.29)	99 (95.19)		
Yes	17 (17.71)	5 (4.81)		
Brain herniation			0.344	0.558
No	93 (96.88)	103 (99.04)		
Yes	3 (3.13)	1 (0.96)		
Cardiac failure			0.504	0.478
No	88 (91.67)	98 (94.23)		
Yes	8 (8.33)	6 (5.77)		
Renal dysfunction			0.872	0.350
No	86 (89.58)	97 (93.27)		
Yes	10 (10.42)	7 (6.73)		
Hepatic cirrhosis			0.185	0.667
No	88 (91.67)	97 (93.27)		
Yes	8 (8.33)	7 (6.73)		
Hypertension			1.307	0.253
No	28 (29.17)	23 (22.12)		
Yes	68 (70.83)	81 (77.88)		
Diabetes			0.649	0.421
No	74 (77.08)	75 (72.12)		
Yes	22 (22.92)	29 (27.88)		
Atrial fibrillation			0.786	0.375
No	84 (87.50)	95 (91.35)		
Yes	12 (12.50)	9 (8.65)		
Use of anticoagulants or antiplatelet agents			10.75	0.001
No	8 (8.33)	27 (25.96)		
Yes	88 (91.67)	77 (74.04)		

PTA (%)	92.06 (85.12, 100.35)	95.65 (87.90, 103.42)	1.599	0.110
PT (s)	12.29 (10.23, 14.19)	10.96 (8.79, 13.02)	2.763	0.006
APTT (s)	26.66 (25.15, 28.65)	26.29 (24.23, 28.52)	1.273	0.203
FBG (g/L)	2.74 (2.45, 3.12)	2.83 (2.50, 3.20)	0.844	0.399
ALP (IU/L)	87.29 (79.95, 97.77)	85.22 (75.38, 93.66)	1.770	0.077
UA (μmol/L)	334.74 (291.36, 377.91)	342.48 (303.88, 395.67)	1.647	0.100
Cr (μmol/L)	86.09 (77.45, 94.44)	82.47 (72.50, 90.87)	1.703	0.089
LDL (mmol/L)	2.21 (1.48, 3.08)	2.74 (1.68, 3.29)	1.912	0.056
HDL (mmol/L)	1.09 (1.00, 1.17)	1.08 (0.98, 1.22)	0.143	0.886
TG (mmol/L)	1.12 (0.76, 1.56)	1.32 (0.82, 1.59)	1.229	0.219
Hcy (μmol/L)	17.29 (10.46, 21.86)	14.40 (8.83, 19.47)	1.684	0.092

BMI: body mass index; GCS: Glasgow Coma Scale; NIHSS: National Institutes of Health Stroke Scale; PTA: prothrombin activity; PT: prothrombin time; APTT: activated partial thromboplastin time; FBG: fibrinogen; ALP: alkaline phosphatase; UA: uric acid; Cr: creatinine; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglycerides; Hcy: homocysteine.

Table 3. Univariate logistic regression analysis of GIB in patients with ischemic stroke

	β	S.E	*P*	OR (95% CI)
Age	0.01	0.01	0.574	1.01 (0.98-1.03)
Gender				
Female				1.00 (Reference)
Male	0.18	0.30	0.539	1.20 (0.67-2.15)
BMI	0.03	0.06	0.621	1.03 (0.92-1.14)
Education level				
Primary school				1.00 (Reference)
Middle and high school	-0.18	0.32	0.569	0.83 (0.45-1.56)
College	-0.30	0.42	0.484	0.74 (0.32-1.71)
GCS score				
15				1.00 (Reference)
13-14	0.26	0.34	0.442	1.30 (0.67-2.52)
9-12	0.74	0.41	0.069	2.10 (0.94-4.67)
3-8	2.06	0.67	0.002	7.88 (2.12-29.32)
NIHSS score				
0-1				1.00 (Reference)
2-4	-0.27	0.38	0.481	0.77 (0.36-1.61)
5-15	0.05	0.37	0.900	1.05 (0.51-2.16)
16-42	0.79	0.58	0.175	2.20 (0.70-6.88)
History of stroke				
No				1.00 (Reference)
Yes	0.27	0.33	0.416	1.31 (0.68-2.53)
History of gastrointestinal disease				
No				1.00 (Reference)
Yes	1.45	0.53	0.006	4.26 (1.51-12.06)
Brain herniation				
No				1.00 (Reference)
Yes	1.20	1.16	0.302	3.32 (0.34-32.50)
Cardiac failure				
No				1.00 (Reference)
Yes	0.40	0.56	0.480	1.48 (0.50-4.45)
Renal dysfunction				
No				1.00 (Reference)
Yes	0.48	0.51	0.354	1.61 (0.59-4.42)

Hepatic cirrhosis				
No				1.00 (Reference)
Yes	0.23	0.54	0.668	1.26 (0.44-3.62)
Hypertension				
No				1.00 (Reference)
Yes	-0.37	0.33	0.254	0.69 (0.36-1.31)
Diabetes				
No				1.00 (Reference)
Yes	-0.26	0.33	0.421	0.77 (0.41-1.46)
Atrial fibrillation				
No				1.00 (Reference)
Yes	0.41	0.47	0.378	1.51 (0.61-3.76)
Use of anticoagulants or antiplatelet agents				
No				1.00 (Reference)
Yes	1.35	0.43	0.002	3.86 (1.65-8.99)
PTA	-0.02	0.01	0.117	0.98 (0.96-1.01)
PT	0.14	0.05	0.004	1.15 (1.05-1.26)
APTT	0.08	0.05	0.086	1.08 (0.99-1.19)
FBG	-0.22	0.29	0.451	0.80 (0.45-1.42)
ALP	0.01	0.01	0.165	1.01 (1.00-1.03)
UA	-0.00	0.00	0.070	1.00 (0.99-1.00)
Cr	0.01	0.01	0.127	1.01 (1.00-1.03)
LDL	-0.24	0.13	0.070	0.79 (0.60-1.02)
HDL	-0.28	0.97	0.774	0.76 (0.11-5.08)
TG	-0.34	0.28	0.216	0.71 (0.41-1.22)
Hcy	0.03	0.02	0.087	1.03 (1.00-1.07)

GIB: gastrointestinal bleeding; BMI: body mass index; GCS: Glasgow Coma Scale; NIHSS: National Institutes of Health Stroke Scale; PTA: prothrombin activity; PT: prothrombin time; APTT: activated partial thromboplastin time; FBG: fibrinogen; ALP: alkaline phosphatase; UA: uric acid; Cr: creatinine; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglycerides; Hcy: homocysteine; OR: odds ratio, CI: confidence interval.

ties (e.g., brain herniation, cardiac failure, renal dysfunction, hepatic cirrhosis, hypertension, diabetes, atrial fibrillation), or other laboratory values ($P>0.05$).

Univariate logistic regression analysis of GIB in patients with ischemic stroke

Univariate logistic regression analysis was conducted to identify risk factors for GIB in patients with ischemic stroke, with GIB occurrence as the dependent variable (cases =1, controls =0). The variables included in the analysis encompassed demographic characteristics (age, gender, BMI, and education level), clinical severity scores (GCS and NIHSS), medical history (e.g., prior stroke and gastrointestinal disease), and comorbidities (e.g., hypertension, diabetes, atrial fibrillation, cardiac failure, renal dysfunction, brain herniation, and hepatic cirrhosis). Medication use, including anticoagulants and antiplatelet drugs, was also considered. Additionally, several laboratory indicators related to coagulation, metabolism, and vascular risk were analyzed. As shown in **Table 3**, a GCS score ≤8 (OR=7.88, 95% confidence interval [95% CI]: 2.12-29.32, P=0.002), a history of gastrointestinal disease (OR=4.26, 95% CI: 1.51-12.06, P=0.006), use of anticoagulants or antiplatelet agents (OR=3.86, 95% CI: 1.65-8.99, P=0.002), and prolonged PT (OR=1.15, 95% CI: 1.05-1.26, P=0.004) were all strongly associated with an increased risk of GIB.

Multivariate logistic regression analysis of GIB bleeding in patients with ischemic stroke

Multivariate logistic regression analysis was conducted, incorporating the significant variables from the univariate analysis. The results

Table 4. Multivariate logistic regression analysis of GIB in patients with ischemic stroke

	β	S.E	*P*	OR (95% CI)
GCS score				
15				1.00 (Reference)
13-14	0.22	0.36	0.549	1.24 (0.61-2.53)
9-12	0.75	0.44	0.085	2.13 (0.90-5.02)
3-8	1.56	0.71	0.029	4.75 (1.18-19.16)
History of gastrointestinal disease				
No				1.00 (Reference)
Yes	1.20	0.59	0.042	3.31 (1.04-10.49)
Use of anticoagulants or antiplatelet agents				
No				1.00 (Reference)
Yes	1.41	0.46	0.002	4.09 (1.68-9.99)
PT	0.14	0.05	0.007	1.15 (1.04-1.28)

GIB: gastrointestinal bleeding; GCS: Glasgow Coma Scale; PT: prothrombin time; OR: odds ratio, CI: confidence interval.

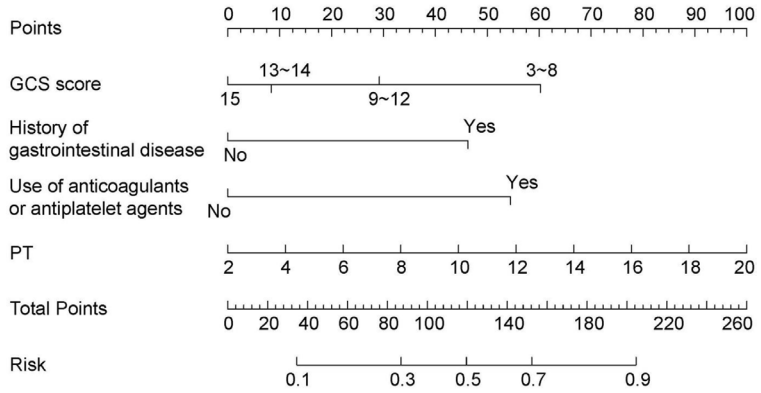

Figure 1. Nomogram for predicting the risk of GIB in ischemic stroke patients. GCS: Glasgow Coma Scale; PT: prothrombin time; GIB: gastrointestinal bleeding.

identified four independent risk factors: a GCS score ≤8 (OR=4.75, 95% CI: 1.18-19.16, *P*=0.029), a history of gastrointestinal disease (OR=3.31, 95% CI: 1.04-10.49, *P*=0.042), use of anticoagulants or antiplatelet agents (OR=4.09, 95% CI: 1.68-9.99, *P*=0.002), and prolonged PT (OR=1.15, 95% CI: 1.04-1.28, *P*=0.007) (P<0.05) (**Table 4**).

Construction of a nomogram predictive model

A nomogram predictive model was established based on the independent risk factors identified in the multivariate logistic regression analysis (**Figure 1**). The model assigns weighted scores to each predictor, facilitating individualized risk estimation for GIB in ischemic stroke patients.

Calibration analysis

In both the training and validation cohorts, the Hosmer-Lemeshow goodness-of-fit test yielded *P*-values of 0.776 and 0.539, respectively, indicating excellent model calibration. This suggested a close fit between the predicted outcomes by the nomogram and the observed outcomes (**Figure 2**).

Diagnostic performance assessment

In the training cohort, the predictive nomogram reached an area under the ROC curve (AUC) of 0.73 (95% CI: 0.66-0.80), while in the validation cohort, the AUC reached 0.79 (95% CI: 0.70-0.89). These results demonstrate that the nomogram model exhibited favorable discriminatory performance in identifying ischemic stroke patients at risk of GIB (**Figure 3**).

Clinical utility assessment

DCA in both the training and validation cohorts showed that the nomogram consistently provided a positive net clinical benefit across a clinically relevant range of threshold probabilities, supporting its potential value as a de cision-support tool in clinical practice (**Figure 4**).

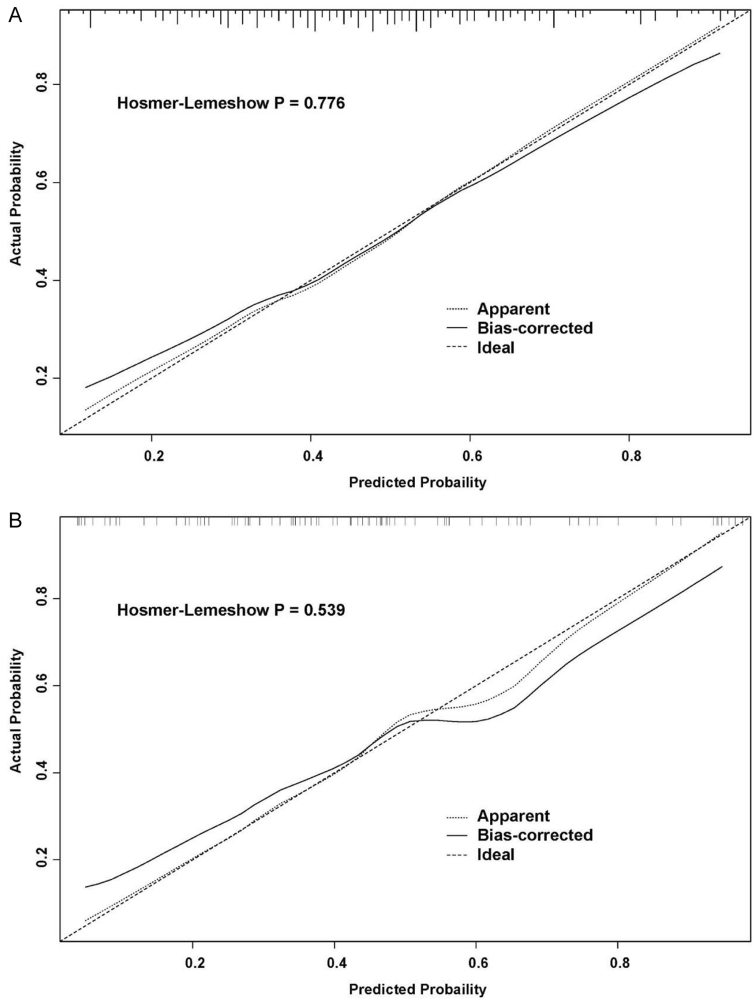

Figure 2. Calibration curves for the nomogram in predicting GIB risk. A: Training cohort; B: Validation cohort. GIB: gastrointestinal bleeding. The x-axis represents the predicted probability of GIB, while the y-axis indicates the actual observed incidence. The diagonal dashed line represents a perfect prediction. The curves showed good agreement between predicted and observed outcomes.

Discussion

Gastrointestinal bleeding (GIB) is a severe complication in patients with ischemic stroke, often leading to prolonged hospitalization, poor prognosis, and increased mortality. Identifying individuals at elevated risk for GIB is crucial for implementing early preventive measures and optimizing therapeutic strategies. However, the multifactorial nature of GIB makes risk prediction challenging in clinical practice. In this context, we conducted a case-control study to systematically investigate the clinical characteristics associated with GIB in ischemic stroke patients and to develop a clinically applicable tool for individualized risk assessment. By focusing on routinely available variables, our aim was to construct a practical model that could assist clinicians in early risk stratification and informed decision-making, ultimately reducing GIB-related complications in this vulnerable population.

Anticoagulant and antiplatelet therapies are fundamental in the secondary prevention of ischemic stroke; however, their ability to increase GIB risk warrants careful consideration [15]. These agents, though effective in reducing thrombotic events, simultaneously impair physiological hemostatic mechanisms, making even minor gastrointestinal mucosal injuries susceptible to significant bleeding [16]. Antiplatelet agents, such as aspirin and clopidogrel, mitigate thrombotic risk by inhibiting platelet aggregation but concurrently diminish the hemostatic integrity of gastrointestinal microvasculature, predisposing mucosal lesions to persistent bleeding [17]. Similarly, blood-thinning drugs like warfarin and dabigatran interfere with the coagulation process, further raising the bleeding risk [18]. A previous study has shown a clear association between prolonged use of these medications and an increased incidence of GIB, especially in stroke patients who remain on these drugs for extended periods [8].

Notably, patients with a history of gastrointestinal disorders may be at increased risk. Even after symptoms are resolved, residual damage to the gut lining may persist, with tissue often remaining fragile and microvessels vulnerable to injury. Therefore, administration of antithrombotic drugs in these patients significantly increases their risk of bleeding [19]. A study by Huang et al. revealed that individuals with a his-

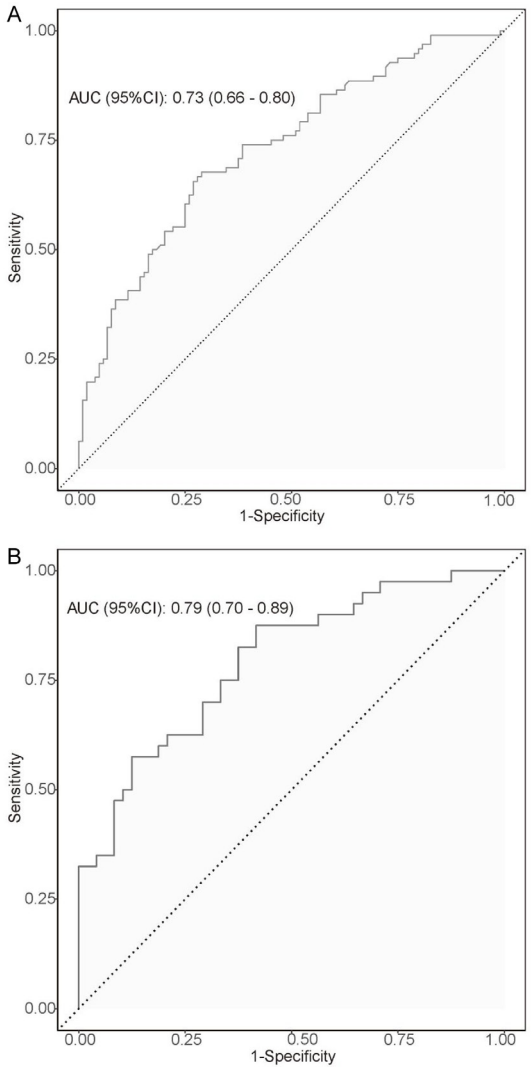

Figure 3. ROC curves assessing the nomogram's discrimination performance. A: Training cohort; B: Validation cohort. ROC: receiver operating characteristic.

tory of ulcers who are treated with blood thinners or antiplatelet agents had a much higher risk of GIB, likely due to the scarring and weakened structure of the gut lining left by old ulcers [20]. Moreover, stroke patients often experience gastrointestinal dysfunctions, including slower digestion, delayed stomach emptying, or altered acid levels [21]. These factors further stress the gut lining, making it more prone to bleeding when combined with blood-thinning treatment [22]. Therefore, it is crucial for clinicians to consider gastrointestinal history when prescribing antithrombotic drugs. A careful review of each patient's digestive health is important, and adjustments to the treatment plan, including protective measures, can help mitigate bleeding risk [23]. Key interventions include the concurrent use of proton pump inhibitors (PPIs) to suppress gastric acid secretion, routine gastrointestinal surveillance for early risk detection, and the development of personalized therapeutic regimens that carefully balance the benefits of antithrombotic therapy with the bleeding risk. Implementing these strategies can significantly improve the safety and efficacy of antithrombotic management in stroke patients [24].

Prolonged PT is commonly indicative of reduced coagulation factor synthesis or functional impairment, which disrupts normal hemostatic mechanisms and renders even minor gastrointestinal mucosal injuries susceptible to persistent bleeding [25]. In this study, PT prolongation was identified as an independent risk factor for GIB. Yuan et al. demonstrated that among stroke patients undergoing anticoagulation therapy, prolonged PT served as a significant predictor of GIB, with this association remaining significant even after adjusting for age and baseline comorbidities [26]. Furthermore, retrospective analyses have suggested that the coexistence of gastrointestinal disorders and coagulation abnormalities may contribute to a "high bleeding risk" state, where increased mucosal fragility and microvascular susceptibility, compounded by impaired coagulation, exacerbate uncontrolled hemorrhage and severe GIB [27]. These findings underscore the role of PT not only as a key biomarker of coagulation status but also as a crucial predictor of GIB in ischemic stroke management. For patients exhibiting significantly prolonged PT, clinicians should carefully optimize anticoagulation regimens while implementing proactive gastric mucosal protection strategies to mitigate bleeding risk.

The GCS is a widely utilized tool for assessing the level of consciousness in ischemic stroke patients, with lower scores indicating more severe neurologic impairment [28]. In this study, a low GCS score was identified as an independent risk factor for GIB in stroke patients. Individuals with lower GCS scores often exhibit significant changes in consciousness, which can impair essential physiologic functions. For instance, they may lose the ability to swallow normally, experience delayed gastric

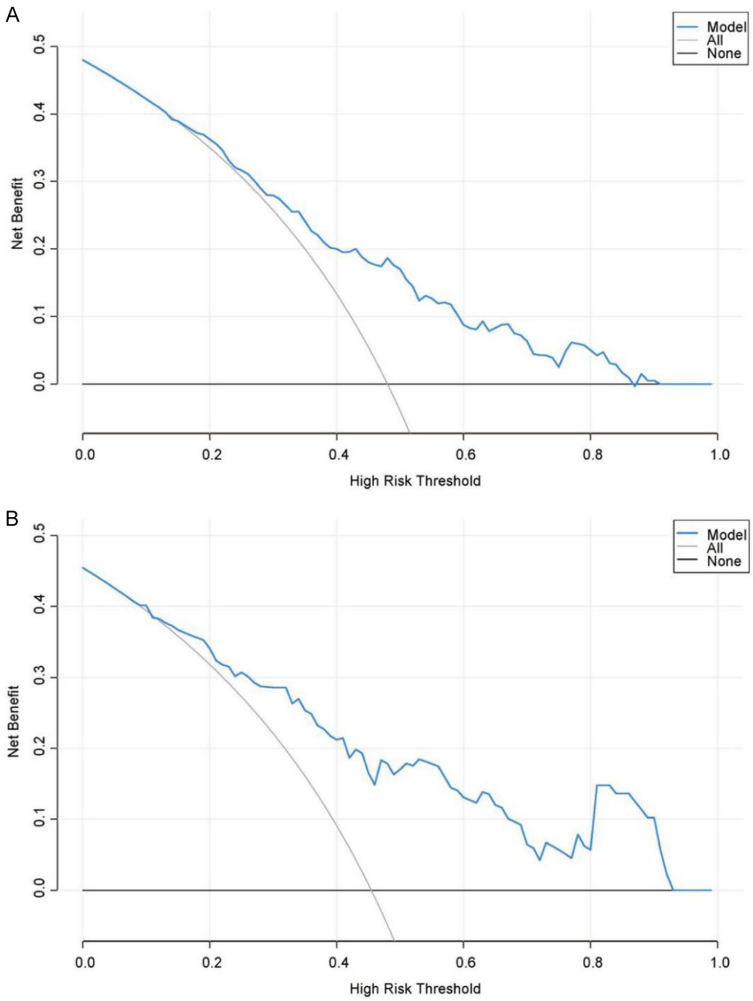

Figure 4. DCA evaluating the clinical utility of the nomogram. A: Training cohort; B: Validation cohort. DCA: decision curve analysis.

emptying, and retain food in the stomach longer than usual. These disruptions can lead to an increase in stomach acid, heightening the risk of developing stress ulcers [29]. In addition, elevated intracranial pressure and an exaggerated stress response can reduce blood flow to the stomach lining, compromising its protective barrier and making patients more susceptible to GIB [30]. Research by Gu et al. demonstrated that patients with a GCS score of ≤8 exhibited significantly impaired gastric motility, prolonged gastric content retention, and increased gastric acid exposure, all of which exacerbate mucosal injury and elevate the risk of gastrointestinal hemorrhage [31]. Additionally, critically ill stroke patients with lower GCS scores often require prolonged nasogastric feeding, and extended gastric tube placement has been shown to further compromise mucosal integrity, increasing the likelihood of bleeding complications [32]. Given these findings, patients with low GCS scores should be considered high-risk for GIB. Early implementation of acid suppression therapy and vigilant gastrointestinal monitoring are essential to mitigate bleeding complications and improve outcomes [33].

In this study, we developed a nomogram incorporating four independent predictors - GCS score ≤8, history of gastrointestinal disease, use of anticoagulant or antiplatelet agents, and prolonged PT - to estimate the risk of GIB in ischemic stroke patients. The model demonstrated acceptable discrimination, with an AUC of 0.73 in the training cohort and 0.79 in the validation cohort, suggesting its potential utility in stratifying patients at high risk and guiding early preventive strategies. Beyond its discriminatory ability, the nomogram also exhibited excellent calibration, as evidenced by non-significant Hosmer-Lemeshow test results in both cohorts, demonstrating good agreement between predicted and observed outcomes. Furthermore, DCA results showed that the model could be useful in clinical practice, offering good net benefits across various threshold probabilities. However, it is important to note that the model's predictions are not flawless. It does not account for several potential factors influencing bleeding risk, such as gastric mucosal damage, *H. pylori* infection, the type and dosage of antithrombotic drugs, and nutritional support. All these factors could significantly affect the risk of GIB [34-36]. As such, the model's accuracy and generalizability might be limited. Incorporating machine learning techniques could help improve the model's performance and broaden its applicability in clinical settings [37].

This study investigated the combined effect of blood clotting abnormalities, neurological impairment, and treatment regimens in assessing the risk of GIB in ischemic stroke patients. By examining the interplay of these factors, we got a clearer picture of the contributors to bleeding risks. The predictive model developed based on these key determinants performed well in risk stratification, offering clinicians an additional tool to guide treatment.

However, several limitations must be considered. First, the data were collected from a single hospital, which may have introduced selection bias and limited the generalizability of the results. Expanding the study to multiple hospitals could enhance its applicability. Second, the predictive capacity of the nomogram was limited by the scope of clinical data available in this study. Future research should try to include more relevant factors to improve the model's predictive accuracy and practical applicability.

Conclusion

In this study, four key factors were identified as independent risk factors for GIB risk in stroke patients: history of gastrointestinal disease, use of anticoagulants or antiplatelet agents, a GCS score of ≤8, and prolonged PT. The predictive model built on these factors effectively distinguished high- and low-risk cases and should help optimize clinical decision-making for individualized patient care.

Disclosure of conflict of interest

None.

Address correspondence to: Qiuming Song, Department of Critical Care Medicine, The Third People's Hospital of Hefei (Hefei Third Clinical College of Anhui Medical University), No. 204 Wangjiang East Road, Baohe District, Hefei 230022, Anhui, China. Tel: +86-0551-63486600; E-mail: sqming1968@163.com

References

[1] Fan J, Li X, Yu X, Liu Z, Jiang Y, Fang Y, Zong M, Suo C, Man Q and Xiong L. Global burden, risk factor analysis, and prediction study of ischemic stroke, 1990-2030. Neurology 2023; 101: e137-e150.

[2] Lu Z, Xiong Y, Feng X, Yang K, Gu H, Zhao X, Meng X and Wang Y. Insulin resistance estimated by estimated glucose disposal rate predicts outcomes in acute ischemic stroke patients. Cardiovasc Diabetol 2023; 22: 225.

[3] GBD 2021 Stroke Risk Factor Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet Neurol 2024; 23: 973-1003.

[4] Aziz MA, Bojja S, Aziz AA, Javed N and Patel H. Gastrointestinal bleeding in patients with acute ischemic stroke: a literature review. Cureus 2024; 16: e53210.

[5] Kim JY, Kim BJ, Kang J, Kim DY, Han MK, Kim SE, Lee H, Park JM, Kang K, Lee SJ, Kim JG, Cha JK, Kim DH, Park TH, Lee K, Park HK, Cho YJ, Hong KS, Choi KH, Kim JT, Kim DE, Choi JC, Oh MS, Yu KH, Lee BC, Park KY, Lee JS, Jang S, Chae JE, Lee J, Kye MS, Gorelick PB and Bae HJ; CRCS-K Investigators. Long-term incidence of gastrointestinal bleeding following ischemic stroke. J Stroke 2025; 27: 102-112.

[6] Martin AC, Benamouzig R, Gouin-Thibault I and Schmidt J. Management of gastrointestinal bleeding and resumption of oral anticoagulant therapy in patients with atrial fibrillation: a multidisciplinary discussion. Am J Cardiovasc Drugs 2023; 23: 407-418.

[7] Ballestri S, Romagnoli E, Arioli D, Coluccio V, Marrazzo A, Athanasiou A, Di Girolamo M, Cappi C, Marietta M and Capitelli M. Risk and management of bleeding complications with direct oral anticoagulants in patients with atrial fibrillation and venous thromboembolism: a narrative review. Adv Ther 2023; 40: 41-66.

[8] Lee AY and Cho JY. Advancements in hemostatic strategies for managing upper gastrointestinal bleeding: a comprehensive review. World J Gastroenterol 2024; 30: 2087-2090.

[9] Abrignani MG, Lombardo A, Braschi A, Renda N and Abrignani V. Proton pump inhibitors and gastroprotection in patients treated with antithrombotic drugs: a cardiologic point of view. World J Cardiol 2023; 15: 375-394.

[10] Zhang J, Zhu S, Liu C, Hu Y, Yang A, Zhang Y and Hong Y. Global, regional and national burden of ischemic stroke attributed to high low-density lipoprotein cholesterol, 1990-2019: a decomposition analysis and age-period-cohort analysis. J Cereb Blood Flow Metab 2024; 44: 527-541.

[11] Komen JJ, Forslund T, Mantel-Teeuwisse AK, Klungel OH, von Euler M, Braunschweig F, Wallén H and Hjemdahl P. Association of preceding antithrombotic therapy in atrial fibrillation patients with ischaemic stroke, intracranial haemorrhage, or gastrointestinal bleed and mortality. Eur Heart J Cardiovasc Pharmacother 2021; 7: 3-10.

[12] Schach C, Reitschuster R, Benedikt D, Füssl E, Debl K, Maier LS and Luchner A. Less major bleeding and higher hemoglobin after left atrial appendage closure in high-risk patients: data from a long-term, longitudinal, two-center observational study. Clin Cardiol 2023; 46: 1337-1344.
[13] Boriani G, Vitolo M and Mei DA. CHA2DS2-VA instead of CHA2DS2-VASc for stroke risk stratification in patients with atrial fibrillation: not just a matter of sex. Europace 2024; 26: euae281.
[14] Collins GS, Reitsma JB, Altman DG and Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015; 350: g7594.
[15] Yan X, Wang B, Xia P, Lan C, Wang Q, Ge W, Zhou Y and Jiang C. Efficacy and safety of anticoagulant therapy versus antiplatelet therapy in acute ischemic stroke patients with atrial fibrillation. Clin Appl Thromb Hemost 2023; 29: 10760296231213070.
[16] Erdoes G, Faraoni D, Koster A, Steiner ME, Ghadimi K and Levy JH. Perioperative considerations in management of the severely bleeding coagulopathic patient. Anesthesiology 2023; 138: 535-560.
[17] Gao Y, Pan Y, Han S, Chen W, Jing J, Wang C, Yang Y, Wang T, Meng X, Zhao X, Liu L, Li H, Johnston SC, Amarenco P, Bath PM, Wang Y and Wang Y; INSPIRES Investigators. Rationale and design of a randomised double-blind 2×2 factorial trial comparing the effect of a 3-month intensive statin and antiplatelet therapy for patients with acute mild ischaemic stroke or high-risk TIA with intracranial or extracranial atherosclerosis (INSPIRES). Stroke Vasc Neurol 2023; 8: 249-258.
[18] McIntyre WF, Benz AP, Becher N, Healey JS, Granger CB, Rivard L, Camm AJ, Goette A, Zapf A, Alings M, Connolly SJ, Kirchhof P and Lopes RD. Direct oral anticoagulants for stroke prevention in patients with device-detected atrial fibrillation: a study-level meta-analysis of the NOAH-AFNET 6 and ARTESiA trials. Circulation 2024; 149: 981-988.
[19] Gu YB, Sun P and Huang WF. Heterotopic gastric mucosa in the jejunum and gastrointestinal bleeding. J Gastrointest Surg 2023; 27: 626-627.
[20] Huang J, Liao F, Tang J and Shu X. Risk factors for gastrointestinal bleeding in patients with cerebral infarction after dual antiplatelet therapy. Clin Neurol Neurosurg 2023; 231: 107802.
[21] Lian Z, Xu Y, Wang C, Chen Y, Yuan L, Liu Z, Liu Y, He P, Cai Z and Zhao J. Gut microbiota-derived melatonin from Puerariae Lobatae Radix-resistant starch supplementation attenuates ischemic stroke injury via a positive microbial co-occurrence pattern. Pharmacol Res 2023; 190: 106714.
[22] Fang CW, Tseng CH, Wu SC, Chen WTL and Muo CH. Association of vagotomy and decreased risk of subsequent ischemic stroke in complicated peptic ulcer patients: an Asian population study. World J Surg 2017; 41: 3171-3179.
[23] Ip YMB, Lau KK, Ko H, Lau L, Yao A, Wong GLH, Yip TCF, Leng X, Chan H, Chan H, Mok V, Soo YOY, Seiffge D and Leung TW. Association of alternative anticoagulation strategies and outcomes in patients with ischemic stroke while taking a direct oral anticoagulant. Neurology 2023; 101: e358-e369.
[24] Greco A, Occhipinti G, Giacoppo D, Agnello F, Laudani C, Spagnolo M, Mauro MS, Rochira C, Finocchiaro S, Mazzone PM, Faro DC, Landolina D, Ammirabile N, Imbesi A, Raffo C and Capodanno D. Antithrombotic therapy for primary and secondary prevention of ischemic stroke: JACC state-of-the-art review. J Am Coll Cardiol 2023; 82: 1538-1557.
[25] Borst AJ, Bonfield CM, Deenadayalan PS, Le CH, Xu M and Reddy SK. Measuring coagulopathy in pediatric craniofacial surgery. Blood Coagul Fibrinolysis 2023; 34: 403-407.
[26] Yuan Y, Li X and Qiu F. Activated partial thromboplastin time or prothrombin time prolongation during rivaroxaban administration: clinical risk factors and outcomes analysis. Clin Appl Thromb Hemost 2023; 29: 10760296231178546.
[27] Zhou D, Li C, Shan J, Guo X, Chen Z, Bai Y and Fan H. Lactobacillus Paragasseri LPG-9 alleviates nsaids-induced gastric ulcers and associated coagulation abnormalities and anemia via the IGF-1/PTEN/Akt/Foxo signaling pathway. Blood 2024; 144: 5472.
[28] Yang JX, Han YJ, Yang MM, Gao CH and Cao J. Risk factors and predictors of acute gastrointestinal injury in stroke patients. Clin Neurol Neurosurg 2023; 225: 107566.
[29] Chen Z, Lin W, Zhang F and Cao W. Risk factors and prognosis analysis of upper gastrointestinal bleeding in patients with acute severe cerebral stroke. J Clin Gastroenterol 2024; 58: 440-446.
[30] Patsalides A, Fargen KM, Davies JM, Boddu SR, Dinkin M, Priest R, Pomeranz HD, Gobin YP and Siddiqui AH. The River study: the first prospective multicenter trial of a novel venous sinus stent for the treatment of idiopathic intracranial hypertension. J Neurointerv Surg 2025; jnis-2024-022540.
[31] Gu Q, Zhu C and Huang J. Risk factors for gastrointestinal bleeding in patients with intrace-

rebral hemorrhage: a propensity score matching analysis. J Clin Neurosci 2024; 127: 110772.
[32] Siddiqui MT, Bilal M, Gollapudi LA, Mehta D, Umar S, Barsa J, Nabors C, Schorr-Lesnick B, Lebovics E and Tewari V. Endoscopy is relatively safe in patients with acute ischemic stroke and gastrointestinal hemorrhage. Dig Dis Sci 2019; 64: 1588-1598.
[33] Qiu W, Liu C, Ye J, Wang G, Yang F, Pan Z, Hu W and Gao H. Age-to-Glasgow Coma Scale score ratio predicts gastrointestinal bleeding in patients with primary intracerebral hemorrhage. Front Neurol 2023; 14: 1034865.
[34] Vakil N. Endoscopic diagnosis, grading, and treatment of bleeding peptic ulcer disease. Gastrointest Endosc Clin N Am 2024; 34: 217-229.
[35] Deguchi S, Iwakami A, Tujigiwa M, Otake H, Mano Y, Yamamoto N, Nakazawa Y, Misra M and Nagai N. Recovery from indomethacin-induced gastrointestinal bleeding by treatment with teprenone. J Pharm Health Care Sci 2023; 9: 44.
[36] Borthwick M, Jenkins B, Wischmeyer PE and Barletta JF. Does enteral nutrition protect against stress ulceration in the critically ill? Curr Opin Clin Nutr Metab Care 2025; 28: 123-128.
[37] Shung DL, Chan CE, You K, Nakamura S, Saarinen T, Zheng NS, Simonov M, Li DK, Tsay C, Kawamura Y, Shen M, Hsiao A, Sekhon JS and Laine L. Validation of an electronic health record-based machine learning model compared with clinical risk scores for gastrointestinal bleeding. Gastroenterology 2024; 167: 1198-1212.