Observational Study

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# Prediction of gastrointestinal bleeding events in patients with acute coronary syndrome undergoing percutaneous coronary intervention

## An observational cohort study (STROBE compliant)

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**Abstract**

Bleeding complications of acute coronary syndromes (ACS) after percutaneous coronary intervention (PCI) are strongly associated with adverse patient outcomes, and gastrointestinal bleeding (GIB) is the most common major bleeding event, especially in the early post-PCI period. Current guidelines recommend routinely conducting bleeding risk assessments. The existing tools are mainly used to evaluate the overall bleeding risk and guide the adjustment of antithrombotic strategies after 1 year. However, there are no specific tools for GIB risk assessment.

Between January 2015 and June 2015, 4943 ACS patients underwent PCI were consecutively enrolled in the derivation cohort. GIB, cardiovascular, and cerebrovascular events were recorded within 1 year of follow-up. A validation cohort including 1000 patients who met the same inclusion and exclusion criteria was also established by propensity-score matching baseline characteristics. Multivariable cox proportional-hazards regression model was used to derive a risk-scoring system, and predictive variables were selected. A risk score nomogram based on the risk prediction model was created to estimate the 1-year risk of GIB.

In this study, we found that the usage of clopidogrel (hazard ratio, HR: 2.52, 95% confidence intervals, CI: 1.573–4.021) and glycoprotein IIb/IIIa receptor inhibitors (HR: 1.863, 95% CI: 1.226–2.829), history of peptic ulcers (HR: 3.601, 95% CI: 1.226–2.829) or tumor (HR: 4.884, 95% CI: 1.226–2.829), and cardiac insufficiency (HR: 11.513, 95% CI: 7.282–18.202), renal insufficiency (HR: 2.010, 95% CI: 1.350–2.993), and prolonged activated partial thromboplastin time (HR: 4.639, 95% CI: 2.146–10.032) were independent risk factors for GIB 1 year after PCI. Based on these 7 factors, a nomogram and scoring system was established. The area under curve of risk score was 0.824 in the deviation cohort and 0.810 in the verification cohort. In both cohorts, the GIB score was significantly better than that of 3 classical bleeding scores (all $P < .05$).

This score could well predict the risk of GIB within 1 year after PCI and could be used to guide antithrombotic strategies.

**Abbreviations:** ACS = acute coronary syndromes, ACTION = acute coronary treatment and intervention outcomes network registry, ACUTIY-HORIZONS = the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) and the HORIZONS-AMI (Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction) trials, aPTT = activated partial thromboplastin time, BARC = bleeding academic research consortium, CABG = coronary artery bypass grafting, CI = confidence intervals, CRUSADE = can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines, DAPT = dual antiplatelet therapy, GIB = gastrointestinal bleeding, GPI = glycoprotein IIb–IIIa receptor inhibitors, HR = hazard ratio, MACCE = major adverse cardiovascular and cerebrovascular events, MI = myocardial infarction, NYHA = New York Heart Association, PCI = percutaneous coronary intervention, PPI = proton-pump inhibitor, PRECISE-DAPT = predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy.

**Keywords:** acute coronary syndrome, gastrointestinal bleeding, percutaneous coronary intervention, prediction score

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*WZ and Y-JZ authors have contributed equally to the study.*

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*Data are available from the authors upon reasonable request and with permission of the third party.*

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## 1. Introduction

Percutaneous coronary intervention (PCI) is the standard treatment for coronary artery occlusion in patients with acute coronary syndrome (ACS). The subsequent dual antiplatelet therapy (DAPT) consists of aspirin and P2Y12 inhibitors to reduce perioperative ischemic complications.[1–3] However, this may increase the risk of bleeding and is linearly related to the duration of DAPT treatment.[4] Studies showed that major bleeding after PCI was associated with increased mortality.[5,6]

Both 2017 ESC and 2016 ACC/AHA (American College of Cardiology/American Hospital Association) guidelines recommended the use of bleeding scoring tools,[7,8] such as DAPT,[9] predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT),[10] and can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines (CRUSADE)[11] risk scores, to guide antithrombotic therapy. The DAPT scoring system can distinguish patients with high bleeding or high ischemic risk. It is mainly used to evaluate whether to extend dual antiplatelet therapy without increasing bleeding risk 1 year after PCI, but it has limited value for risk assessment within 1 year in the real world.[12] Therefore, the DAPT score is only applicable to patients with low-risk hemorrhagic disease who can tolerate DAPT for 1 year after PCI. The CRUSADE score is a good predictor of in-hospital major bleeding after PCI. These scoring systems are mainly used to assess the overall risk of bleeding, including a variety of major bleeding events, such as intracranial and gastrointestinal bleeding (GIB).[9,10,13] Obviously, the incidence and causes of different bleeding events are different, so the overall assessment is limited.[12,14]

Many studies have shown that the assessment of bleeding risk should be highly individualized. For example, patients with a history of gastrointestinal ulcers are more likely to have gastrointestinal bleeding,[15] while patients with cerebral aneurysms are more likely to have intracranial hemorrhage. Targeted assessment of major bleeding events could help doctors to make a more accurate judgment according to the actual situation of patients. In addition, the gastrointestinal tract is the most common site of postoperative massive bleeding. Therefore, it is urgent to establish an independent GIB risk assessment tool after PCI to fill this gap.

## 2. Patients and methods

### 2.1. Study design and derivation cohort

The patient population involved in this study included a derivation cohort and a validation cohort, all from Beijing Anzhen Hospital. This study was approved by the Ethics Committee of our hospital (No. 2018055X). The derivation cohort in this study consecutively enrolled patients over 18 years of age who were hospitalized for acute coronary syndrome from January to June 2015. The cohort initially enrolled 9186 patients, excluding patients with incomplete information or who could not be followed up within 1 year (256) and patients undergoing coronary artery bypass grafting (CABG, N = 2340) or conservative treatment (N = 1647). Four thousand nine hundred forty three patients eventually entered the derivation cohort. Two doctors are responsible for collecting and recording the patient's demographic and clinical characteristics, treatment, and laboratory examination information during hospitalization. The sample size calculation in this study is based on the sample size estimation method of the diagnostic test, using "Tests for one-sample sensitivity and specificity" analysis in the PASS software (NCSS, LLC, USA). We set the parameters as: power is 0.9, alpha is 0.05, the prevalence (GIB incidence) is 4%, the minimum specificity is 0.7, and the expected specificity is 0.8.

### 2.2. Clinical endpoints and definitions

In this study, only the first bleeding event of each patient was considered. GIB is defined as clinical events (coffee-ground emesis, hematemesis, melena, or hematochezia) recorded by a physician or endoscopic evidence indicating active bleeding in the upper or lower gastrointestinal tract. GIB events within 1 year were categorized according to the Bleeding Academic Research Consortium (BARC) classifications. Myocardial infarction (MI) was defined according to the Fourth universal definition of myocardial infarction. Definite/probable ST were defined according to the Academic Research Consortium criteria. Unplanned revascularization was defined as any unexpected coronary revascularization procedure or coronary artery bypass graft surgery (CABG) during the follow up. Stroke diagnosis was confirmed by a treating neurologist. Computed tomography or magnetic resonance imaging was used to distinguish ischemic from hemorrhagic stroke.

### 2.3. Follow up

From the index PCI to 1 year, we followed up all patients through rehospitalization, outpatient review or telephone contact to assess bleeding complications, major adverse cardiovascular and cerebrovascular events (death, myocardial infarction, unplanned revascularization, or stroke). Survival and event data come from hospital records and statements from the patients themselves or family members. The records include demographic information, examinations, medications, and surgical information. In addition, the detailed medication situation at the time of the GIB incident was also recorded in detail.

### 2.4. Validation cohort

An external validation of the model was done in an additional 1000 patients. These patients were admitted between January and March 2017 in Beijing Anzhen Hospital, who met the same enrollment criteria and were matched for baseline characteristics by propensity score. Meanwhile, patients enrolled in the derivation cohort were excluded. The information collection, follow-up, and endpoint definitions were similar with the derivation cohort. We calculated CRUSADE,[11] acute coronary treatment and intervention outcomes network registry (ACTION),[16] and the Acute Catheterization and Urgent Intervention Triage strategY and the HORIZONS-AMI (Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction) trials (ACUTIY-HORIZONS)[17] bleeding risk scores in both cohorts for performance evaluation of predictive models.

### 2.5. Statistical analysis

Descriptive data is reported as mean ± standard deviation (SD) or frequency as a percentage. We used the Kaplan–Meier method to estimate the probability of GIB, screened demographic

information, clinical characteristics, comorbidities, testing, and medication information one by one to find potential predictors that might affect GIB ($P < .10$). A Cox proportional hazards regression model was used for multivariate analysis, and an independent GIB predictor was selected by backward selection ($P < .05$). At the same time, considering that some antithrombotic drugs may have a significant impact on the occurrence of GIB, even if the model cannot be optimally fitted, it should be forced into the model. In multiple regression analysis, we verified the proportional hazards hypothesis through time correlation test and residual plot check. This Cox model is the basis of the nomogram. Through ROC curve analysis, the optimal cut-off point of continuous variables were found and converted into categorical variables. Linear predictor values are scaled and rounded to integer values (between 0 and 30), and performance is evaluated by the trail-specific Harrell C index. The ability to identify patients at high bleeding risk was visualized by Kaplan–Meier cumulative bleeding incidence curves in bleeding risk score quartiles. Calibration was assessed by comparing predicted probabilities with actual 1-year Kaplan–Meier GIB incidence estimates. Calibration is assessed by plotting the predicted probabilities against the actual outcome. The graph obtained should be like a 45° line if the predictions are well calibrated. Furthermore, discrimination and calibration of the GIB risk score were assessed in the external validation cohort. We did all analyses using R software (3.6) and SPSS version 25 (SPSS Inc., Chicago, IL).

## 3. Results

### 3.1. Baseline characteristics

The validation cohort used the similar inclusion and exclusion criteria with the derivation cohort, and the main clinical characteristics were matched by propensity scores, so the baselines of the 2 groups were comparable (Table 1). The only difference was that the proportion of patients who used ticagrelor over clopidogrel and who used bivalirudin increased over time (both $P < .001$).

**Table 1**

**Baseline characteristics.**

| Variables | Derivation cohort (N = 4943) | Validation cohort (N = 1000) | *P* value |
|---|---|---|---|
| Demographics | | | |
| Age, y | 57.56 ± 10.04 | 57.83 ± 11.05 | .47 |
| Men | 3823 (77.3) | 769 (76.9) | .095 |
| BMI | 26.21 ± 3.28 | 27.29 ± 5.13 | <.001 |
| Medical history | | | |
| Prior PCI | 617 (12.5) | 117 (11.7) | .493 |
| Prior CABG | 84 (1.7) | 18 (1.8) | .823 |
| Hypertension | 2558 (51.7) | 522 (52.20) | .795 |
| Diabetes mellitus | 1563 (31.62) | 298 (29.8) | .258 |
| Hyperlipemia | 2038 (41.23) | 402 (40.20) | .546 |
| Prior myocardial infarction | 294 (5.95) | 70 (7.0) | .206 |
| Stroke or TIA | 202 (4.1) | 46 (4.6) | .148 |
| Renal insufficiency/failure | 94 (1.90) | 19 (1.9) | .997 |
| Malignancy | 66 (1.34) | 13 (1.30) | .929 |
| Peptic ulcer/GIB | 281 (5.68) | 57 (5.70) | .985 |
| Anemia | 755 (15.3) | 155 (15.5) | .856 |
| Atrial fibrillation | 12 (0.2) | 6 (0.6) | .061 |
| Thrombolysis | 40 (0.8) | 6 (0.6) | .491 |
| Cardiac function | | | |
| Class I | 4459 (90.21) | 890 (89.0) | .558 |
| Class II | 369 (7.47) | 81 (8.1) | |
| Class III | 77 (1.56) | 21 (2.1) | |
| Class IV | 38 (0.77) | 8 (0.8) | |
| Diagnosis | | | |
| NSTE-ACS | 3830 (77.5) | 781 (78.1) | .670 |
| STEMI | 1113 (22.5) | 219 (21.9) | |
| Laboratory tests | | | |
| Hemoglobin, g/dL | 141.2 ± 14.36 | 141.18 ± 14.56 | .963 |
| White-blood-cell counts, $10^9$/L | 6.90 ± 1.79 | 6.98 ± 1.77 | .181 |
| Platelet counts, $10^9$/L | 212.84 ± 59.02 | 218.65 ± 55.11 | .004 |
| PT, s | 10.79 ± 2.55 | 10.75 ± 1.23 | .686 |
| aPTT, s | 33.26 ± 8.69 | 32.76 ± 4.83 | .083 |
| ALT, U/L | 32.95 ± 41.55 | 32.12 ± 24.35 | .528 |
| AST, U/L | 28.02 ± 28.78 | 27.53 ± 19.28 | .603 |
| BUN, mmol/L | 5.44 ± 2.19 | 5.38 ± 2.02 | .483 |
| eGFR, ml/min/1.73 $m^2$ | 93.21 ± 27.76 | 92.8 ± 27.92 | .675 |
| Antithrombotic therapy | | | |
| Clopidogrel | 2624 (53.1) | 449 (44.9) | <.001 |
| Ticagrelor | 2319 (46.9) | 551 (55.1) | |
| GIIb/IIIa receptor inhibitors | 966 (19.5) | 173 (17.3) | .100 |
| Aspirin | 4942 (99.98) | 1000 (100) | .653 |
| Warfarin | 5 (0.10) | 1 (0.10) | .992 |
| LMWH/Fondaparinux | 2833 (57.3) | 576 (57.6) | <.001 |
| Bivalirudin | 52 (1.1) | 44 (4.4) | <.001 |

ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BMI = body mass index, CABG = coronary artery bypass grafting, eGFR = estimated glomerular filtration rate, GIB = gastrointestinal bleeding, LMWH = low molecular weight heparin, NSTE-ACS = non–ST-segment elevation acute coronary syndromes, PCI = percutaneous coronary intervention, PT = prothrombin time, STEMI = ST-segment elevation myocardial infarction, TIA = transient ischemic attacks.

### 3.2. Medication

In terms of antithrombotic treatment, 57.3% (2833/4943) of patients used low molecular heparin or fondaparinux before the first PCI procedure; 19.5% (966/4943) of patients used Glycoprotein IIb–IIIa receptor inhibitors (GPI) during the perioperative period; almost all patients used DAPT before the bleeding events. Among them, 53.1% (2624/4943) of patients used clopidogrel and 46.1% (2319/4943) of patients used ticagrelor. At 1 year of follow-up, 90.7% (4483/4943) of patients continued to take DAPT, 23.7% (550/2319) of patients who had previously used ticagrelor switched to clopidogrel; 3.5% (92/2624) of patients who had previously used clopidogrel switched to ticagrelor. In the prevention of gastrointestinal bleeding, 95.5% (4720/4943) of patients during the perioperative period and during hospitalization used intravenous or oral proton-pump inhibitor (PPI) drugs.

### 3.3. Events

During the 1-year follow-up, 512 cases of bleeding events occurred in the derivation cohort, including 102 cases of gastrointestinal bleeding, 10 cases of intracranial hemorrhage, 12 cases of fundus hemorrhage, 339 cases of gum bleeding, nose bleeding or subcutaneous bleeding, 6 cases of hemoptysis, and 23 cases of hematuria, 1 case of retroperitoneal bleeding, and 19 cases of bleeding at the puncture site. During the follow-up, the derivation cohort cumulatively reported 137 major adverse cardiovascular and cerebrovascular events (MACCE), including 60 cases of recurrent myocardial infarction, 22 cases of repeat revascularization, 21 cases of stroke, and 49 all-cause deaths.

**Table 2**

**Multivariate analysis of gastrointestinal bleeding events in the derivation cohort.**

| Variables | $\beta$ estimate | HR (95% CI) | *P* value |
|---|---|---|---|
| Cardiac dysfunction (NYHA class III/IV) | 2.443 | 11.513 (7.282–18.202) | <.001 |
| eGFR < 80 mL/min•1.73 $m^2$ | 0.698 | 2.010 (1.350–2.993) | .001 |
| History of tumor | 1.586 | 4.884 (2.236, 10.671) | <.001 |
| History of peptic ulcer/GIB | 1.281 | 3.601 (2.285, 5.673) | <.001 |
| Clopidogrel (ref. as ticagrelor) | 0.922 | 2.515 (1.573, 4.021) | <.001 |
| GPI | 0.622 | 1.863 (1.226, 2.829) | .004 |
| aPTT > 40 s | 1.535 | 4.639 (2.146, 10.032) | .007 |

aPTT = activated partial thromboplastin time, CI = confidence interval, eGFR = estimated glomerular filtration rate, GIB = gastrointestinal bleeding, GPI = glycoprotein IIb/IIIa receptor inhibitors, HR = hazard ratio, NYHA = New York Heart Association.

### 3.4. Development of a predictive score

During 1-year follow-up, 102 (2.1%) and 17 (1.7%) GIB events occurred in derivation and validation cohort, respectively. Predictors with a *P* value <.10 at univariable analysis were included in the multivariable model. From the multivariate analyses (Table 2), we developed a 7-item GIB risk score including perioperative medication (GPI, $P2Y_{12}$), renal function, heart function, coagulation function and medical history (ulcer and tumor) at baseline and assigned points to each factor based on the magnitude of association of each predictor with GIB. A nomogram to calculate the score and the risk of GIB at 12 months is presented in Fig. 1. The prediction rule for the GIB risk assigned 1 point for GPI usage (during and after PCI), 1 point for eGFR <80 mL/min•1.73 $m^2$, 1 point for clopidogrel usage (loading and continuous use, reference as ticagrelor usage), 2 points for activated partial thromboplastin time (aPTT) >40 seconds, 2 points for medical history of peptic ulcer, 2 points for medical history of tumor, and 3 points for heart failure (New York Heart Association, NYHA class III/IV heart failure).

### 3.5. Evaluation of the GIB risk score

The calibration of the model was tested in the derivation cohort and proved satisfactory. Calibration measures a model's ability to generate predictions that are on average close to the average observed outcome. We use the calibration curve to assess calibration. Figure 2 shows the nomogram-predicted GIB was well calibrated with the Kaplan–Meier-observed GIB.

The discrimination of the model was tested in both cohorts. The GIB risk score showed a Harrell c-index of 0.828 (SD 0.045) in the derivation cohort. Therefore, 82.5% of the time the nomogram correctly predicted the ordering of the outcome between 2 randomly selected patients. The AUC for the GIB risk score was 0.824 (SE 0.023) in the derivation cohort and 0.810 (SE 0.050) in the validation cohort (Fig. 3). There were significant differences between the GIB score and other scores including CRUSADE, ACTION, and HORIZONS scores (GIB vs CRUSADE, 0.824 vs 0.715, $P < .01$; GIB vs ACTION, 0.824 vs 0.764, $P = .042$; GIB vs HORIZONS, 0.824 vs 0.693, $P < .01$) in the derivation cohort. There were larger AUC for GIB score than other 3 scores in the validation cohort (all $P < .05$). The GIB score was validated with modest accuracy in the validation cohort without significant difference in area under the curve (AUC) between the derivation and validation cohorts ($P = .39$).

There was close correlation of predictive score and GIB risk. In both the derivation and validation cohorts, the GIB incidence was markedly higher in patients with high risk scores (score ≤2: 0.37% vs 0.24%; score 3–4: 1.53% vs 1.84%; score ≥5: 14.15% vs 7.69%; Fig. 4). We selected the best cutoff point based on the AUC curve (which maximizes the sum of sensitivity and specificity) as a high-risk segmentation point (≥5 points).

### 3.6. Subgroup analysis

In the subgroup analysis, according to the occurrence time of GIB, GIB events occurring within 30 days are defined as early GIB

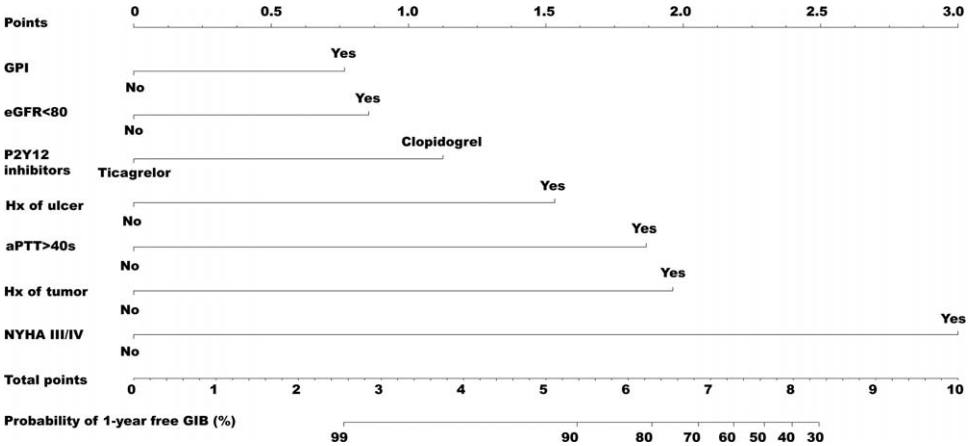


**Figure 1.** Nomogram to predict the risk of 1-year gastrointestinal bleeding. A multivariate analysis of GIB-free survival was conducted to generate the nomogram in the derivation cohort. Predictors include usage of GPI or P2Y12 inhibitors, eGFR <80 mL/min•1.73 $m^2$, aPTT > 40 seconds, medical history of peptic ulcer or tumor, and NYHA class III/IV. Draw a line above the "points" line for the corresponding values of these factors, calculate the sum of these 7 points, and draw on the "total points" line for 1-year GIB-free survival risk. aPTT = activated partial thromboplastin time, eGFR = estimated glomerular filtration rate, GIB = gastrointestinal bleeding, GPI = glycoprotein IIb–IIIa receptor inhibitors, NYHA = New York Heart Association.

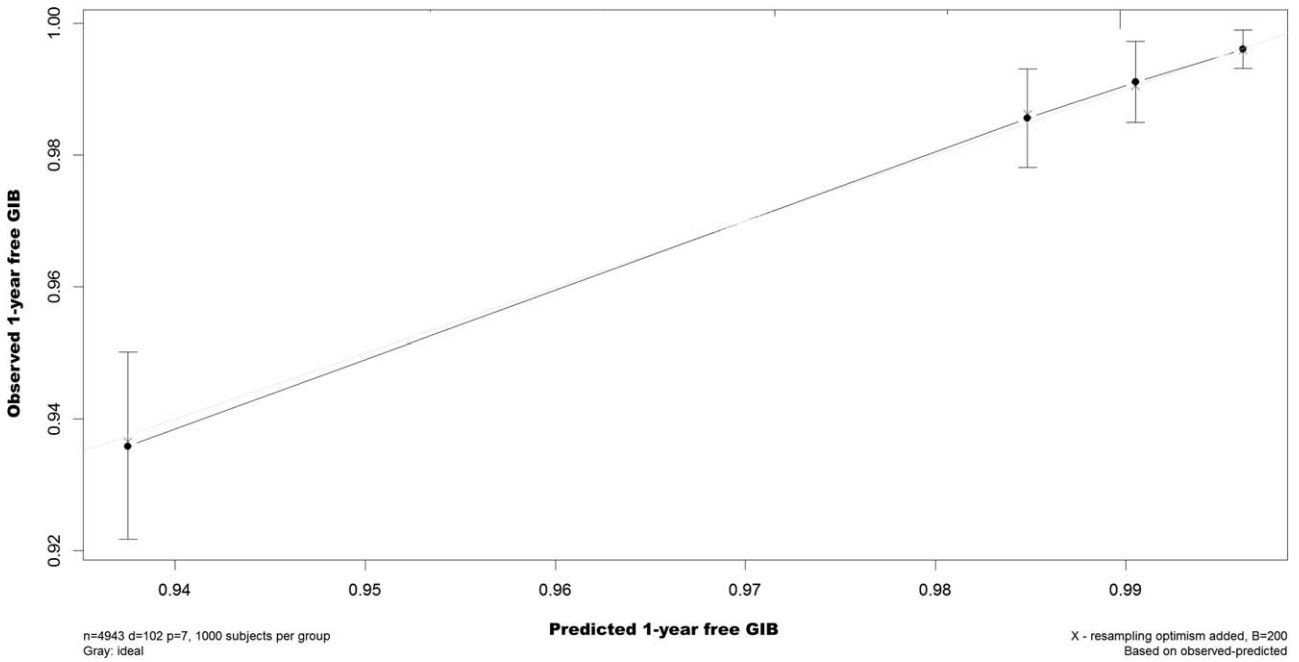


**Figure 2.** Calibration curve of nomogram-predicted GIB-free survival. The *x*-axis represents the nomogram-predicted probability of GIB-free survival; the *y*-axis represents the actual GIB-free probability. Plots along the 45° line indicate a perfect calibration model in which the predicted probabilities are identical to the actual outcomes. Vertical bars indicate 95% confidence intervals. GIB = gastrointestinal bleeding.

events, and GIB events occurring within 30 days to 1 year are defined as late GIB events. Multivariate Cox regression analysis showed early GIB events significantly associated with advanced age (HR: 1.024, 95% CI: 1.000–1.049), history of tumor (HR: 3.702, 95% CI: 1.582–8.665), history of peptic ulcer (HR: 2.682, 95% CI: 1.617–4.449), eGFR $< 80\,mL/min \bullet 1.73\,m^2$ (HR: 1.874, 95% CI: 1.156–3.038), aPTT >40 seconds (HR: 6.023, 95% CI: 2.436–14.895), heart rate increase (HR: 1.019, 95% CI: 1.005–1.033), moderate to severe cardiac insufficiency (HR: 8.055, 95% CI: 4.799–13.520), ST-segment elevation myocardial infarction (HR: 2.759, 95% CI: 1.750–4.351), and clopidogrel usage (HR: 2.670, 95% CI: 1.578–4.518). Late GIB events were only significantly related to the history of peptic ulcer disease (HR: 11.135, 95% CI: 3.643–34.037). Patients with GIB events had a significantly higher rate of MACCE than those without GIB events (13.7% vs 2.5%, $P < .001$).

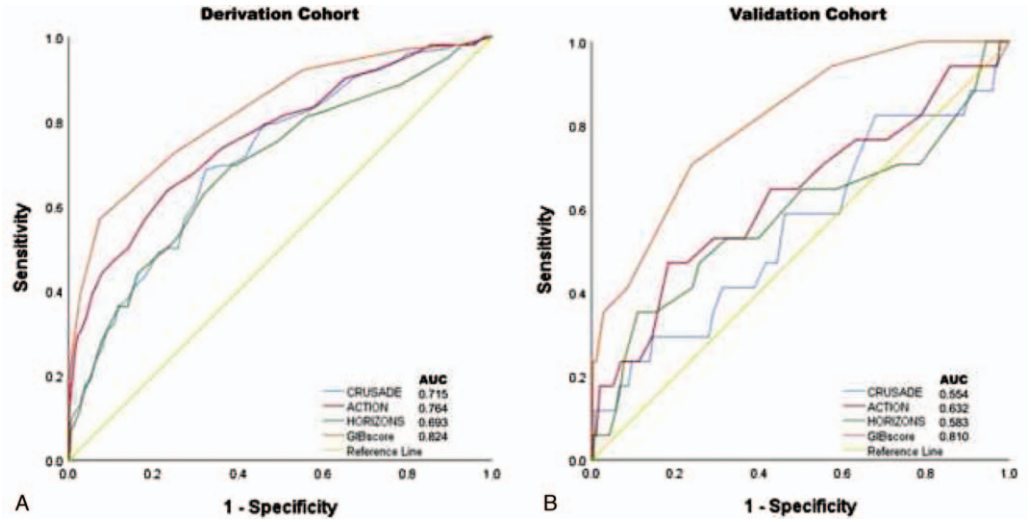


**Figure 3.** Discriminatory accuracy for predicting GIB assessed by receiver operator characteristics (ROC) analysis calculating area under the curve (AUC). 1-year GIB risk prediction in the derivation cohort, compared with 3 other classical bleeding scores (A). 1-year GIB risk prediction in the validation cohort, compared with 3 other classical bleeding scores (B). ACTION = the Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines risk score; CRUSADE = the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcome with Early Implementation of the American College of Cardiology/American Heart Association Guidelines risk score; GIB = gastrointestinal bleeding; HORIZONS = the Acute catheterization and urgent intervention triage strategy and The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction bleeding risk score.

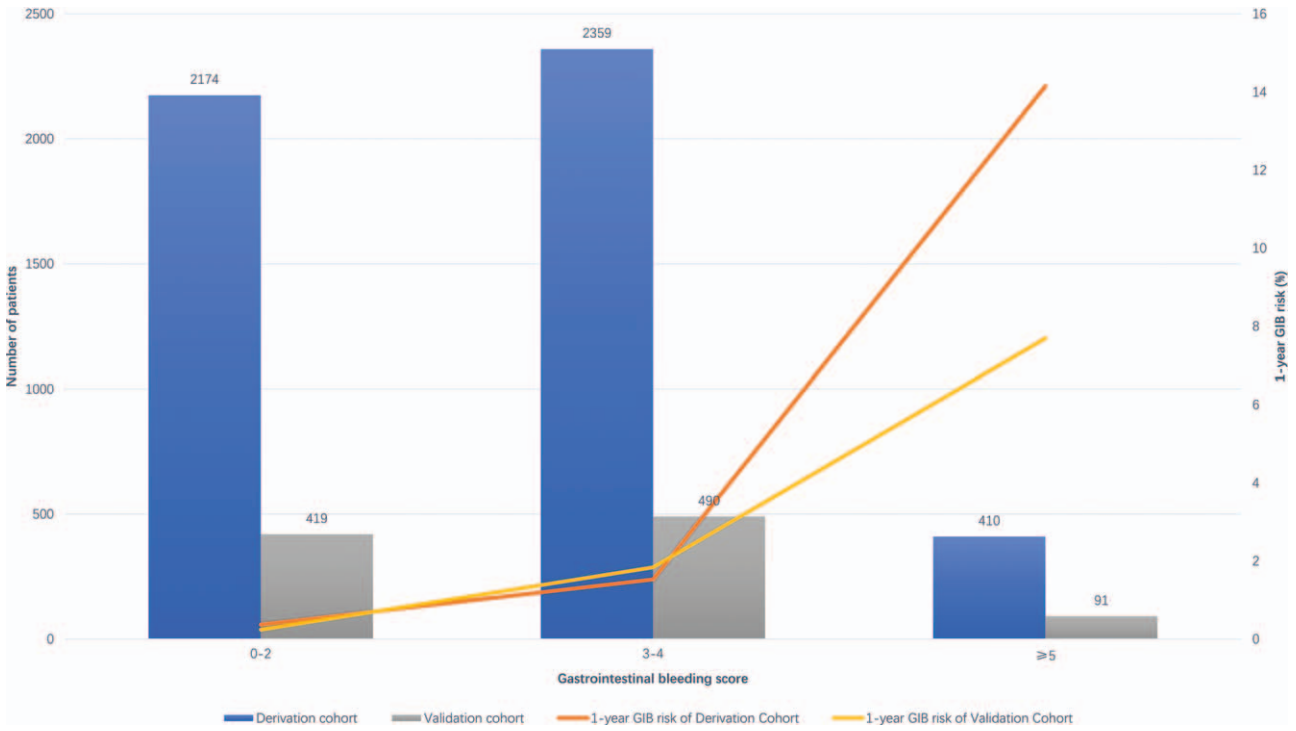


**Figure 4.** Distribution of the prediction scores in the derivation and validation cohorts. The risk curves show the incidences of 1-year GIB in the different prediction scoring groups. The histogram shows the GIB score distribution in the derivation and validation cohorts. GIB = gastrointestinal bleeding.

## 4. Discussion

In this study, we found that the use of clopidogrel and GPI, history of gastrointestinal ulcers or tumors, and cardiac insufficiency, renal insufficiency, and prolonged aPTT time were independent risk factors for GIB 1 year after PCI. Based on these 7 risk factors, we established a GIB risk assessment model. As the model score increases, the incidence of GIB increases significantly. The results of validation cohort show that the score can distinguish patients with high gastrointestinal bleeding within 1 year after PCI, and its prediction accuracy is better than classic scores such as CRUSADE, ACTION, and HORIZONS.

Several previous studies have suggested that the above 7 factors are related to the occurrence of GIB events after PCI. The 2015 ESC defined the characteristics of high-risk patients with GIB, including a history of GIB or anticoagulant use.[18] Karim et al[19] noted that patients with a history of previous GIB had increased re-bleeding and mortality after PCI, and had a higher rate of anemia, heart failure, and sudden cardiac death, with approximately 40% requiring endoscopic therapy. Zhang et al[20] pointed out that patients with a history of digestive ulcers had a higher rate of upper gastrointestinal bleeding after PCI. The use of PPI is an effective preventive and therapeutic approach.[21,22] APTT is a key indicator for monitoring the effect of anticoagulants, and prolongation may be related to perioperative anticoagulant treatment.[23] High-dose or multi-drug combined anticoagulation may cause acute gastrointestinal bleeding after PCI. Zhu et al[24] indicated that renal dysfunction was an independent risk factor of post-discharge 1-year GIB after PCI. Similarly, Gaglia et al[25] found that variables associated with increased risk of GIB included older age, shock, acute myocardial infarction, chronic renal insufficiency, lower baseline hematocrit, and glycoprotein IIb/IIIa inhibitors in their study. Patients with large myocardial infarction and heart failure are more likely to develop gastrointestinal bleeding. Gastrointestinal function alterations occur in patients with heart failure as a result of low cardiac output and increased central venous pressure. The incidence of GIB was 3.2% of the 2103 heart failure patients.[26] These views are similar to the results of our study.

Some limitations of our research should be considered. First, the patients in the derivation and validation cohort come from the same hospital and belong to a single-center study. Inevitably, there will be insufficient selectivity and external verification. However, the enrollment time and personnel of the 2 cohorts did not overlap, which could reduce this bias to some extent. In addition, the patients included in this study were mainly in East Asian population. Previous studies suggest that the risk of ischemia in anti-platelet therapy is higher in the East Asian population than in the Caucasian population.[27] So the extrapolation of this study has certain limitations. Of course, it will be more suitable for East Asian populations. Second, the baseline information did not include *Helicobacter pylori* infection, CYP450 gene polymorphism, and detailed surgical information, but we collected a history of peptic ulcer or hemorrhage, puncture site, stent implantation, and perioperative antithrombotic medication. Some patients in this study had information on *H pylori* infection (15%) and CYP450 gene polymorphism (62%) at baseline. Subgroup analysis did not suggest that the above 2 factors could significantly affect the occurrence of GIB. Third, the model can predict the risk of GIB bleeding in patients, but unlike DAPT or PRECISE-DAPT studies, this study does not provide further antithrombotic treatment strategies. The key role of the score is to identify patients at high GIB risk and provide evidence for their prophylactic use of antiulcer drugs and adjustment of antithrombotic treatment strategies.

## 5. Conclusion

We developed and validated the GIB score, a simple 7-item algorithm used to predict the risk of gastrointestinal bleeding in ACS patients within 1 year after PCI. This score can specifically identify and distinguish high-risk patients with GIB, which is superior to traditional scoring models, and is used to guide the selection of antithrombotic treatment strategies after PCI. A multi-center validation study of this score can be conducted in future clinical practice.

## Author contributions

Wen Zheng developed the analysis plan and undertook the data analysis and the writing of the paper. Yu-Jiao Zhang guided the statistical analysis of the results. Ran Liu and Xue-Dong Zhao collected the dataset and provided advice on its analysis. Hui Ai guided the analysis and made substantial improvements to the paper. Hui Ai and Wen Zheng supervised the study and contributed to the data analysis plan.

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