Received: 10 April 2019 | Accepted: 21 April 2019
DOI: 10.1002/ccd.28325

WILEY

ORIGINAL STUDIES

A risk score to predict postdischarge bleeding among acute coronary syndrome patients undergoing percutaneous coronary intervention: BRIC-ACS study

Yundai Chen[1] | Tong Yin[1] | Shaozhi Xi[1] | Shuyang Zhang[2] | Hongbing Yan[3] | Yida Tang[4] | Juying Qian[5] | Jiyan Chen[6] | Xi Su[7] | Zhimin Du[8] | Lefeng Wang[9] | Qin Qin[10] | Chuanyu Gao[11] | Yang Zheng[12] | Xianxian Zhao[13] | Xiaoshu Cheng[14] | Zhanquan Li[15] | Wenqi Zhang[16] | Hui Chen[17] | Jingping Wang[18] | Zhiming Yang[19] | Hui Li[20] | Heping Liu[21] | Xuchen Zhou[22] | Baiming Qu[23] | Dingcheng Xiang[24] | Ying Guo[25] | Lin Wang[26] | Shaoping Nie[27] | Guosheng Fu[28] | Ming Yang[29] | Shanglang Cai[30]

[1]Department of Cardiology, General Hospital of Chinese People's Liberation Army, Beijing, China

[2]Department of Cardiology, Peking Union Medical College Hospital, Beijing, China

[3]Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Beijing, China

[4]Department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[5]Department of Cardiology, Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai, China

[6]Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

[7]Department of Cardiology, Wuhan Asia Heart Hospital, Wuhan, China

[8]Cardiology Department, First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

[9]Heart Canter, Beijing Chao Yang Hospital, Capital Medical University, Beijing, China

[10]Department of Cardiology, Tianjin Chest Hospital, Tianjin, China

[11]Department of Cardiology, Zhengzhou University People's Hospital (Henan Provincial People's Hospital), Zhengzhou, China

[12]Department of Cardiology, The First Hospital of Jilin University, Changchun, China

[13]Department of Cardiovasology, Changhai Hospital, Second Military Medical University, Shanghai, China

[14]Department of Cardiology, Second Affiliated Hospital, Nanchang University, Nanchang, China

[15]Department of Cardiology, The People's Hospital of Liaoning Province, Shenyang, China

[16]Department of Cardiology, China-Japan Union Hospital of Jilin University, Changchun, China

[17]Cardiovascular Center, Capital Medical University, Beijing Friendship Hospital, Beijing, China

[18]Department of Cardiology, Shanxi Cardiovascular Hospital, Taiyuan, China

[19]Department of Cardiology, The Second Hospital of Shanxi Medical University, Taiyuan, China

[20]Department of Cardiology, Daqing Oilfield General Hospital, Daqing, China

[21]Department of Cardiology, Jilin Province People's Hospital, Changchun, China

[22]Department of Cardiology, First Affiliated Hospital of Dalian Medical University, Dalian, China

[23]Department of Cardiology, Zhejiang Provincial People's Hospital, Hangzhou, China

[24]Department of Cardiology, General Hospital of Guang Zhou Military Command, Guangzhou, China

[25]Department of Cardiology, Hunan Provincial People's Hospital, Changsha, China

[26]Department of Cardiology, Tongji Hospital , Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

[27]Emergency & Critical Care Center, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

[28]Department of Cardiology, Biomedical Research (Therapy) Center, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China
[29]Department of Cardiology, Fuxing Hospital Affiliated to Capital Medical University, Beijing, China
[30]Department of Cardiology, Affiliated Hospital of Qingdao University, Qingdao, China

Correspondence
Yundai Chen, Department of Cardiology, General Hospital of Chinese People's Liberation Army, No. 28 Fu Xing Road, Beijing 100853, China.
Email: cyundai@vip.163.com

Funding information
Sanofi

Abstract

Background: Dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) prevents ischemic events while increasing bleeding risk. Real-world-based metrics to accurately predict postdischarge bleeding (PDB) occurrence and its potential impact on postdischarge major cardiovascular event (MACE) remain undefined. This study sought to evaluate the impact of PDB on MACE occurrence, and to develop a score to predict PDB risk among Chinese acute coronary syndrome (ACS) patients after PCI.

Methods and Results: From May 2014 to January 2016, 2496 ACS patients who underwent PCI were recruited consecutively from 29 nationally representative Chinese tertiary hospitals. Among 2,381 patients (95.4%, 2,381/2,496) who completed 1-year follow-up, the cumulative incidence of PDB (bleeding academic research consortium type [BARC] ≥2) and postdischarge MACE (a composite of all-cause death, nonfatal myocardial infarction, ischemic stroke, or urgent revascularization) was 4.9% (n = 117) and 3.3% (n = 79), respectively. The association between PDB and MACE during 1-year follow-up, as well as the impact of DAPT with ticagrelor or clopidogrel on PDB were evaluated. PDB was associated with higher risk of postdischarge MACE (7.7 vs. 3.1%; adjusted hazard ratio: 2.59 [95% confidence interval: 1.17–5.74]; p = .02). For ticagrelor versus clopidogrel, PDB risk was higher (8.0 vs. 4.4%; 2.05 [1.17–3.60]; p = .01), while MACE risk was similar (2.0 vs. 3.4%; 0.70 [0.25–1.93]; p = .49). Based on identified PDB predictors, the constructed bleeding risk in real world Chinese acute coronary syndrome patients (BRIC-ACS) score for PDB was established. C-statistic for the score for PDB was 0.67 (95% CI: 0.62–0.73) in the overall cohort, and >0.70 in subgroups with non-ST- and ST-segment elevation myocardial infarction, diabetes and receiving more than two drug eluting stents.

Conclusions: In Chinese ACS patients, PDB with BARC ≥2 was associated with higher risk for MACE after PCI. The constructed BRIC-ACS risk score provides a useful tool for PDB discrimination, particularly among high ischemic and bleeding risk patients.

KEYWORDS
antiplatelet therapy, bleeding, coronary artery disease, percutaneous coronary intervention

1 | INTRODUCTION

Dual antiplatelet therapy (DAPT), that is, aspirin and a P2Y12 inhibitor, prevents thrombotic complications following percutaneous coronary intervention (PCI) with drug-eluting stents (DES) of acute coronary syndrome (ACS).[1] Current guidelines recommend use of newer potent P2Y12 inhibitors such as prasugrel or ticagrelor for 12 months after an ACS managed with PCI.[2] However, the greatest anti-ischemic benefit of potent antiplatelet drugs over clopidogrel occurs early, while most excess bleeding events, as the most common complication, arise predominantly during the maintenance phase.[3,4] While the impact and contribution of postdischarge bleeding (PDB) events on late mortality has been documented,[5,6] the relationship between PDB and postdischarge ischemic events remains undefined.

To date, most bleeding risk scores (e.g., CRUSADE or ACUITY) for ACS or PCI patients have focused on in-hospital events or short-term risk.[7–10] Although these scales are useful to inform clinical decisions regarding periprocedural antithrombotic therapies or other bleeding avoidance strategies, their utility with respect to long-term use of DAPT is less certain.[11] Moreover, the underlying risk factors or their respective weights may vary for early as opposed to later bleeding events.[8,12] To this end, PRECISE-DAPT was developed and recommended to evaluate the benefits and risks of different DAPT durations based on randomized clinical trials.[2,13,14] However, randomized

trials may underestimate the "real-world" incidence of clinically important bleeding events in ACS,[15] underscoring the need for stratification tools focusing on PDB events during the chronic phase of DAPT use, that is, within 12 months in a real-world clinical setting. We therefore evaluated the incidence, predictors, and impact of PDB on post-discharge major adverse cardiovascular events (MACE) in ACS patients who underwent successful DES implantation in the large-scale registry of bleeding risk in real world Chinese acute coronary syndrome patients (BRIC-ACS) study. We also sought to develop a dedicated risk score specifically designed to predict risks for PDB events within 12 months of follow-up to improve risk assessment and support clinicians' decisions with respect to personalized DAPT.

2 | METHODS

2.1 | Study population

The BRIC-ACS study was a nationwide, multicenter, prospective registry specifically designed to evaluate the bleeding risk in Chinese ACS patients who underwent PCI. In brief, 2,520 ACS patients who underwent PCI during admission were prospectively and consecutively enrolled at 29 tertiary centers between May 2014 and January 2016 (see Supporting Information).[16,17] All patients were treated according to usual clinical practice at each site, while one or more DES were successfully implanted using standard techniques followed by clopidogrel or ticagrelor alongside aspirin therapy. Patients were excluded if any of the following criteria was met: ACS as a secondary diagnosis; inability to give informed consent or to undergo 1-year of follow-up; pregnancy or breastfeeding; and lost to follow-up after discharge. Clinical follow-up was scheduled at 1, 3, 6, and 12 months by phone interview or personal contact. Standardized questions were used to assess bleeding episodes, thrombotic events, and use of medications. Data on bleeding events and MACE, as well as medication and pharmacy dispensation data, were collected. A blinded and independent clinical events committee of 5–10 cardiologists held a meeting for adjudicating all clinical outcome events (PDB and MACE), using the original records and phone-call recording, according to the BARC standardized bleeding criteria[18] and the definitions of MACE. Institutional review board approval was obtained at each participating center, and all patients signed written informed consent prior to enrollment.

2.2 | Study objectives and definitions

The objectives of the present study were to evaluate the effect of PDB on the postdischarge MACE within 1 year, and finally to develop a bleeding risk score for predicting PDB risk within 1 year.

According to the BARC standardized bleeding Criteria[18] developed by a consensus effort of academics, research organizations, industry, and regulator representatives for cardiovascular clinical trials, PDB was defined as clinical-related bleeding occurring after hospital discharge following successful DES implantation with a BARC type ≥2 bleeding event (excluding BARC type 4). The following prespecified bleeding site categories were used: gastrointestinal, intracranial, subcutaneous, genitourinary, hemoptysis, and others.

Other outcomes also evaluated in the present study included BARC type ≥3 bleeding events (excluding BARC type 4), BARC type 1 bleeding events, MACE (a composite of all-cause mortality, non-fatal myocardial infarction [MI], urgent coronary revascularization [CRV] and ischemic stroke). All-cause mortality was defined as death due to definite cardiovascular factors, or due to any other noncardiovascular events. Nonfatal MI was diagnosed according to the diagnostic criteria laid down in the updated ESC guidelines[2,19] including non-ST-segment elevation myocardial infarction (Non-STEMI) and ST-segment elevation myocardial infarction (STEMI). Urgent CRV was defined as re-hospitalization due to ACS that causes PCI or CABG to be performed within 24 hr.[2] Ischemic stroke was defined as neurologic focal impairment due to an ischemic event, with symptoms persisting for at least 24 hr, resulting in death.

2.3 | Statistical analysis

We calculated that assuming 10 parameters in the final model, 10–15 positive bleeding events could be detected for each parameter, an event rate of PDB of 6.8%[20] and a dropout rate of 10%, at least 2,451 patients would be required to develop a novel bleeding risk model.

Descriptive statistics are presented as median (IQR) and were compared using the Kruskal–Wallis test; while categorical variables are reported as *n* (%) and were compared using the Chi-square test or Fisher's exact test. Outcomes based on time to first event were assessed by comparison of Kaplan–Meier-based cumulative incidence rates with the log-rank test. COX regression analysis (with time-dependent covariates) was used for univariable and multivariable analyses, with time of first occurrence of PDB, MACE, or all-cause mortality as the dependent outcome in each model. Forest plots were also generated for visual inspection.

We also studied the associations between possible predictors and PDB using Cox regression analysis stratified by trial. Potential predictors of PDB were selected using univariable analysis ($p < .15$). Both the identified potential predictors and other candidate variables potentially associated with bleedings based on a comprehensive literature review and clinical plausibility were included in the multivariable analysis, then independent PDB predictors were selected using multivariable backward selection ($p < .05$). Curvilinear predictor values were scaled and rounded to a score with integer values between 0 and 60. Patients were then grouped into levels of low, intermediate, and high risk, with thresholds reflecting clinically meaningful (at least 3.5-fold) gradients in risk from one group to the next. Discrimination of the bleeding risk score was assessed by the receiver operating characteristic curve.[21] The primary model was internally validated using the method of Markov Chain Monte Carlo with bootstrap resampling for 200,000 iterations. For each 10 resampling, one random resampling result was extracted. Then the mean value of each regression coefficient was compared with that from the direct fitting model. Moreover, the model also was validated in analyses of subgroups stratified by ACS type, sex, age, diabetes as comorbidity, and number of implanted DES.

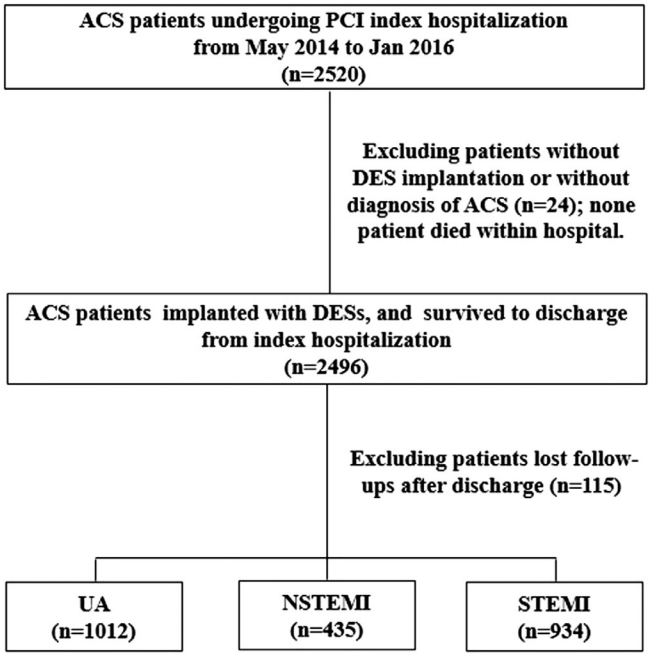


FIGURE 1 Study flow chart

Statistical significance was defined as $p < .05$. SAS software 9.4 and SPSS software 22.0 were used for statistical analyses.

3 | RESULTS

3.1 | Incidence and sites of PDB

Among 2,520 patients enrolled in BRIC-ACS study with definitive diagnosis of ACS and who underwent PCI with DES, 2,381 eligible patients were included in the current analysis: 1,012 patients (42.5%) with unstable angina (UA), 435 patients (18.3%) with NSTEMI and 934 patients (39.2%) with STEMI (Figure 1). During 1-year follow-up, 117 patients (4.9%) suffered PDB, including 101 with BARC type 2 bleeding, while 19 patients (0.8%) experienced BARC type ≥3 bleeding. The most common site of PDB was gastrointestinal (Figure 2). Risk of bleeding accrued over time, and PDB primarily occurred in the early period (<90 days), with a rate of first bleeding of 2.0% (47/2,381) and a proportion of 40.2% (47/117).

3.2 | Impact of PDB on postdischarge MACE

During 1-year follow-up, 79 patients (3.3%) experienced MACE, including 56 patients (2.4%) with all-cause mortality (24 cardiac mortality), 17 patients with ischemic stroke, and 11 patients with nonfatal MI or urgent CRV. Risk of MACE accrued over time, with MACE occurring primarily in the early period (<90 days); rate of first MACE was 1.6% (37/2,381) with proportion of 46.8% (37/79).

Relative to patients without PDB, patients experiencing PDB had higher unadjusted rate of the 1-year clinical outcome of MACE after discharge (7.7 vs. 3.1%, $p = .01$). Figure 3 shows unadjusted rates for the composite outcome according to PDB occurrence. After adjustment for demographic characteristics, comorbid conditions, triple-vessel lesion, and DAPT strategies (including clopidogrel alongside aspirin, ticagrelor alongside aspirin, and DAPT discontinuation for >1 month), PDB was significantly associated with higher risk of post-discharge MACE (adjusted hazard ratio [HR], 2.59; 95% confidence interval [CI]: 1.17–5.74; $p = .02$; Figure 3). No significant association was found between PDB and all-cause mortality during 1-year follow-up (Table 1).

3.3 | Establishment and validation of the BRIC-ACS score for PDB prediction

In terms of baseline clinical characteristics (Table 2), patients with PDB within 1 year were older, more commonly female, more likely with lower body mass index (BMI) or hemoglobin and with higher prevalence of hypertension or prior peptic ulcer. Patients experiencing PDB also were more likely to have had received low-molecular-weight heparin within 48 hr pre-PCI or treated with ticagrelor alongside aspirin. Relative to patients treated with clopidogrel ($n = 1,813$), those treated with ticagrelor ($n = 199$) had a significantly higher risk for PDB (4.4 vs. 8.0%, adjusted HR: 2.05, 95% CI: 1.17–3.60, $p = .01$) but not

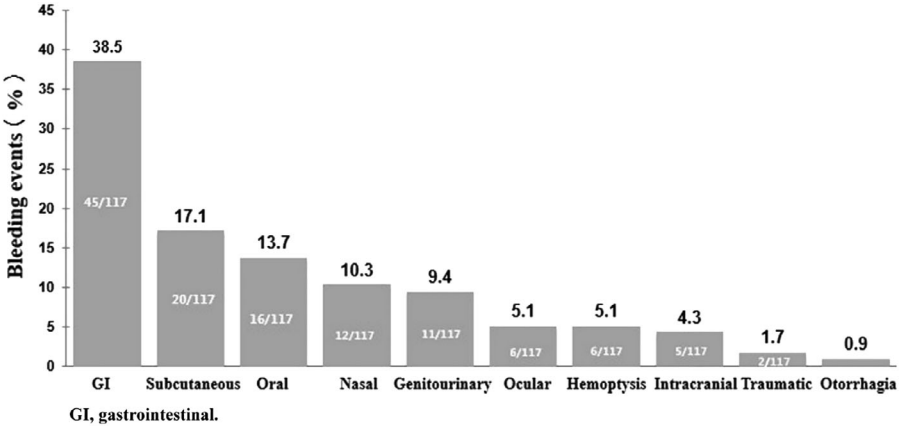
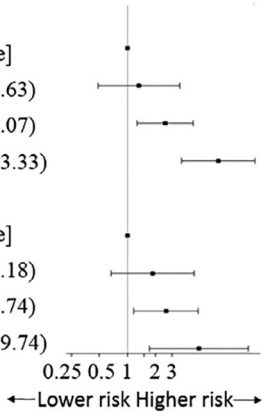


FIGURE 2 Site of postdischarge bleeding with bleeding academic research consortium (BARC) ≥2

Subgroup	No. of Events/ Person years	Annual Events/ Rate(95%CI)	HR(95%CI)	P Value
Unadjusted				
No clinical relevant bleeding	70/2217.7	3.2(2.5-4.0)	1[Reference]	
BARC =2	4/95.5	4.2(1.6-11.2)	1.32(0.48-3.63)	.5851
BARC ≥2	9/111.8	8.0(4.2-15.5)	2.53(1.27-5.07)	.0087
BARC ≥3	5/16.3	30.7(12.8-73.7)	9.41(3.80-23.33)	<.0001
Adjusted				
No clinical relevant bleeding	70/2217.7	3.2(2.5-4.0)	1[Reference]	
BARC =2	4/95.5	4.2(1.6-11.2)	1.85(0.67-5.18)	.2369
BARC ≥2	9/111.8	8.0(4.2-15.5)	2.59(1.17-5.74)	.0189
BARC ≥3	5/16.3	30.7(12.8-73.7)	5.83(1.72-19.74)	.0047



Adjusted factors included age, hypertension, diabetes , chronic renal failure, peripheral vascular diseases, triple-vessel lesion, heart failure, ACS (UA vs. STEMI/NSTEMI), and different DAPT strategy. BARC, Bleeding Academic Research Consortium.

FIGURE 3 Impact of different types of postdischarge bleeding on postdischarge major cardiovascular event (MACE)

for MACE (3.4 vs. 2.0%, adjusted HR: 0.70, 95% CI: 0.25–1.93, p = .49; Figure 4).

From multivariable analysis, the factors independently associated with PDB included sex × multivessel lesion, BMI, hemoglobin, triglycerides, low-density lipoprotein cholesterol (LDL-C) at baseline, hypertension, prior peptic ulcer, and ticagrelor alongside aspirin. Point estimates and corresponding 95% CI for each covariate are shown in Table 3. The strongest predictor for PDB, quantified and ranked using the p value, was administration of ticagrelor alongside aspirin.

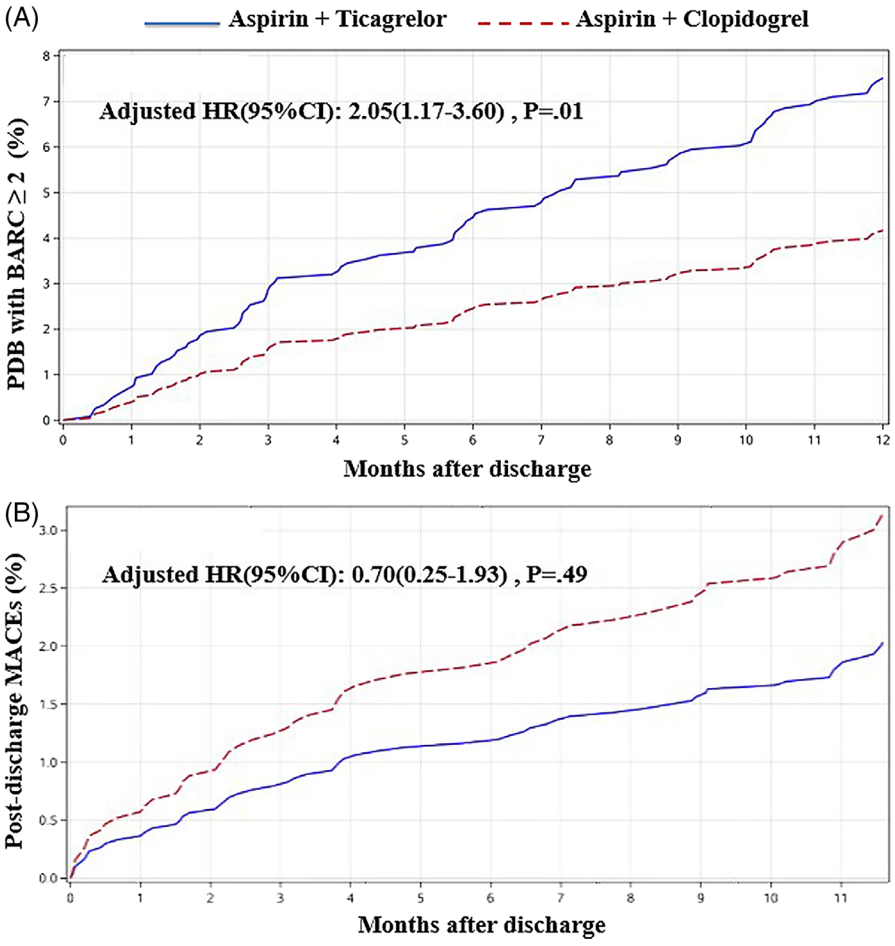


FIGURE 4 Adjusted cumulative incidences of (panel A) PDB with BARC ≥2, (panel B) postdischarge MACE according to subgroups receiving continuous ticagrelor or clopidogrel therapy. BARC, bleeding academic research consortium; MACE, major cardiovascular event; PDB, postdischarge bleeding. Adjusted factors included age, sex, BMI, hypertension, diabetes, history of peptic ulcer, and ACS (STEMI/NSTEMI vs. UA). Aspirin + Clopidogrel is the reference category [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Impact of postdischarge bleeding and ischemic events on 1-year all-cause mortality

	Number of patients	Number of deaths	Unadjusted annual mortality rate (per 100 person-year)	Unadjusted HR (95%CI)	Unadjusted *p* value	Adjusted HR (95%CI)[a]	Adjusted *p* value
BARC ≥2 bleedings	117	5	4.4	1.87 (0.75–4.68)	.18	1.68 (0.66–4.28)	.28
BARC ≥3 bleedings	19	3	16.9	7.20 (2.25–23.04)	.001	5.93 (1.63–21.52)	.007
Stroke	17	2	12.4	5.17 (1.26–21.18)	.02	1.71 (0.37–7.86)	.49
Nonfatal MI and urgent revascularization	17	2	20.0	12.60 (3.94–40.31)	.000	11.90 (2.75–51.43)	.001

Abbreviations: BARC, BARC, bleeding academic research consortium; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.
[a]Adjusted for age, hypertension, diabetes, chronic renal insufficiency, peripheral vascular diseases, triple-vessel lesion, heart failure, ACS (UA vs. STEMI/NSTEMI).

TABLE 2 Comparison of clinical data between patients with and without PDB

	Postdischarge BARC ≥2 bleeding (*n* = 117)	No postdischarge BARC ≥2 bleeding (*n* = 2,264)	*p*-Value
Demographic data			
Age, median (IQR), y	63 (56, 72)	61 (53, 68)	.019
Female, *n* (%)	40 (34.2)	521 (23.0)	.006
BMI, median (IQR), kg/m^2	25 (22,26)	25 (23, 27)	.008
≥25 kg/m^2	37 (31.6)	937 (41.4)	.037
Current drinker, *n* (%)	18 (15.5)	453 (20.2)	.219
Medical history, n (%)			
Coronary artery disease	36 (30.8)	649 (28.8)	.646
Congestive heart failure	2 (1.7)	23 (1.0)	.472
Hypertension	78 (66.7)	1,296 (57.2)	.044
Diabetes mellitus	31 (26.5)	591 (26.2)	.943
Chronic renal insufficiency	5 (4.3)	55 (2.4)	.217
Cerebrovascular disease	6 (5.1)	169 (7.5)	.339
Prior peptic ulcer	10 (8.5)	109 (4.8)	.072
Prior vascular disease[a]	2 (1.7)	25 (1.1)	.551
Prior-PCI	12 (10.3)	237 (10.5)	.942
Clinical presentation (%)			
ACS type			
STEMI	44 (37.6)	890 (39.3)	.713
NSTEMI	15 (12.8)	420 (18.6)	.118
UA	58 (49.6)	952 (42.0)	.108
NYHA/KILLIP class ≥ II	31 (26.5)	587 (25.9)	.891
Admission data and laboratory evaluation			
Heart rate, median (IQR), bpm	71 (65, 80)	72 (64, 80)	.767
SBP, median (IQR). mm Hg	130 (117, 138)	130 (117,141)	.598
LVEF, median (IQR), %	58 (52, 63)	60 (53,65)	.123
Hemoglobin, median (IQR), g/dL	135 (122, 145)	140 (129,150)	.0005
Baseline hematocrit, median (IQR), %	40 (37, 43)	41 (38,44)	.017
WBC, median (IQR) × 10^9/L	7 (6, 9)	8 (6,10)	.151
Platelet count, median (IQR) × 10^9/L	208 (176, 239)	210 (173,252)	.668
Creatinine clearance[b], median (IQR) mL/min	75 (62, 101)	88 (67,109)	.033
<60 mL/min	20 (20.4)	305 (16.56)	.320

(Continues)

TABLE 2 (Continued)

	Postdischarge BARC ≥2 bleeding (*n* = 117)	No postdischarge BARC ≥2 bleeding (*n* = 2,264)	*p*-Value
Lesion and procedure characteristics (%)			
Left main lesion	5 (4.3)	78 (3.4)	.634
Triple-vessel lesion	13 (11.1)	322 (14.2)	.345
Multivessel lesion	55 (47.0)	1,255 (55.4)	.074
Chronic total occlusion,	41 (35.0)	851 (37.6)	.579
Urgent/direct PCI	30 (25.6)	592 (26.1)	.903
Vascular access site			
Femoral	14 (12.0)	256 (11.3)	.823
Radial	100 (85.5)	1972 (87.1)	.608
Closure device used	11 (9.7)	222 (9.9)	.956
Number of DESs≥2	40 (34.5)	970 (43.4)	.058
Perioperative antithrombotic treatment n (%)			
LMWH administered within 48 hr pre-PCI	5 (4.3)	37 (1.6)	.034
GPIIb/IIIa inhibitor	30 (27.0)	479 (22.0)	.212
UFH/ enoxaparin +GP IIb/IIIa inhibitor	27 (23.1)	421 (18.6)	.227
Bivalirudin +GP IIb/IIIa inhibitor	0 (0.0)	9 (0.4)	1.000
Bivalirudin monotherapy	0 (0.0)	45 (2.0)	.168
Antithrombotic treatment after discharge, n (%)			
Continuous ticagrelor	17 (14.5)	184 (8.1)	.015
Continuous clopidogrel	80 (68.4)	1,768 (78.1)	.014
Warfarin, at discharge	1 (0.9)	9 (0.4)	.456
TAT at discharge[c]	1 (0.9)	7 (0.3)	.320
Concomitant medications, n (%)			
Statins	61 (52.1)	1,125 (49.7)	.606
Gastric acid inhibitor	33 (28.2)	697 (30.8)	.555
β-Blockers	76 (65.0)	1,416 (62.5)	.599
Calcium-channel blocker	23 (19.7)	389 (17.2)	.490
RAS inhibitors	64 (54.7)	1,204 (53.2)	.748

Abbreviations: ACS, acute coronary syndrome; BARC, bleeding academic research consortium; BMI, body mass index; DES, drug-eluting stent; LMWH, low-molecular-weight heparin; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PDB, postdischarge bleeding; RAS, renin-angiotensin system; SBP, Systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; UFH, unfractionated heparin; WBC, white blood cell.

[a]Referring to a history of cerebrovascular disease and/or peripheral artery disease.

[b]Creatinine clearance was calculated with the Cockcroft-Gaut formula.

[c]TAT referred to three antithrombotic therapy, including aspirin, clopidogrel, and warfarin or dabigatran.

Based on the multivariable model, we assigned points to each factor and then developed a 9-item bleeding risk score—the BRIC-ACS score (Table 4). The score was calculated using the following formula: Z score = 64.49 + 3.06 × sex + 8.97 × prior peptic ulcer + 5.56 × hypertension − 2.62 × multivessel lesion + 8.47 × ticagrelor alongside aspirin − 0.72 × BMI − 0.12 × hemoglobin − 11.97 × $\log_{10}$ triglycerides − 5.13 × $\log_{10}$ LDL-C. The sum of the weighted integer (range 1–60 points) estimates the risk of PDB within 1 year. The BRIC-ACS score distribution in the derivation cohort and the risk of PDB in 1 year is presented in Figure 5. The BRIC-ACS score had moderate ability to discriminate between patients who did and did not have a PDB (*c*-statistic, 0.67 [95%CI, 0.62–0.73]). After bootstrap internal validation, optimism-corrected *c*-statistics was also 0.67 (95%CI, 0.62–0.73; Table 5). The rates of PDB for BRIC-ACS score distribution tertiles were 1.2% (low risk: 0–20 points), 4.7% (moderate risk: 21–39 points), and 17.3% (high risk: 40–60 points; *p* trend <.0001; Figure 6).

The performance of the BRIC-ACS bleeding score was also validated in subgroups of the cohort displaying relatively good discriminatory ability in the subgroups of patients with NSTEMI, STEMI, diabetes, or implantation of >2 DES (*c*-statistic, ≥0.70; Table 5). However, the risk score showed relatively poor discriminatory power for patients 75 years or older (*c*-statistic, 0.63; Table 5).

TABLE 3 Independent predictors of PDB during 1 year of follow-up

Variables	HR (95%CI)	*p*-Value
Sex × multivessel lesion	1.236 (1.017–1.502)	.033
BMI	0.931 (0.880–0.985)	.013
Prior peptic ulcer	2.461 (1.210–5.006)	.013
Hypertension	1.742 (1.100–2.757)	.018
Hemoglobin	0.988 (0.978–0.997)	.012
Triglycerides	0.305 (0.120–0.772)	.012
LDL-C	0.598 (0.393–0.911)	.017
Ticagrelor alongside aspirin	2.318 (1.240–4.334)	.009

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; LDL-C, low density lipoprotein cholesterol; PDB, postdischarge bleeding.

TABLE 4 The BRIC-ACS score algorithm for bedside application

Variable	Score
Sex	0-male, 1-female
Prior peptic ulcer	0-no, 1-yes
Hypertension	0-no, 1-yes
Multivessel lesion	0-no, 1-yes
Ticagrelor alongside aspirin	0-no, 1-yes
BMI	Actual value
Hemoglobin	Actual value
Triglycerides	$\log_{10}$triglycerides
LDL-C	$\log_{10}$ LDL-C

Note: *Z* score = 64.49 + 3.06 × sex + 8.97 × prior peptic ulcer + 5.56 × hypertension − 2.62 × multivessel lesion + 8.47 × ticagrelor alongside aspirin − 0.72 × BMI − 0.12 × hemoglobin − 11.97 × $\log_{10}$ triglycerides − 5.13 × $\log_{10}$ LDL-C.
Abbreviations: BMI, body mass index; BRIC-ACS, bleeding risk in real world Chinese acute coronary syndrome patient; LDL-C, low density lipoprotein cholesterol.

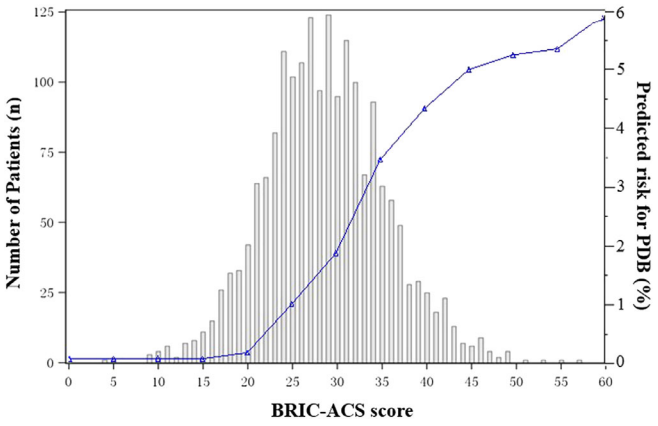


FIGURE 5 Distribution of the bleeding risk in real world Chinese acute coronary syndrome patients (BRIC-ACS) risk score and corresponding predicted risk for postdischarge bleeding (PDB) in the overall patient population [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 5 Validation of the BRIC-ACS score in the overall cohort by bootstrap resampling method and subgroups

Groups	AUC (95%CI)
Overall cohort	0.67 (0.62–0.73)
UA	0.62 (0.54–0.70)
NSTEMI	0.80 (0.64–0.95)
STEMI	0.71 (0.61–0.81)
Women	0.67 (0.58–0.76)
Men	0.66 (0.58–0.73)
Age ≥75 y	0.63 (0.45–0.82)
Age <75 y	0.67 (0.61–0.74)
Diabetes	0.71 (0.60–0.81)
No diabetes	0.66 (0.59–0.73)
Number of DESs ≤2	0.67 (0.60–0.73)
Number of DESs >2	0.71 (0.55–0.87)

Abbreviations: AUC, area under the curve; BRIC-ACS, bleeding risk in real world Chinese acute coronary syndrome patient; DES, drug-eluting stent; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

4 | DISCUSSION

The BRIC-ACS study is the first nationwide, multicenter, prospective registry specifically designed to evaluate the PDB risk in Chinese ACS patients who underwent PCI. The main findings of the present analysis of data derived from the BRIC-ACS study are: PDB was strongly associated with postdischarge MACE within 1 year; The BRIC-ACS bleeding risk score, developed for the prediction of PDB within 1 year in ACS patients who underwent PCI and with contemporary use of two oral P2Y12, provides a useful tool particularly in patients with high ischemic and bleeding risk.

In the all-comers BRIC-ACS population, PDB occurred in approximately 1 of every 20 patients within 1 year of follow-up, with slightly more than one third of PDB events occurring within 90 days. Consistent with prior studies,[6,22,23] gastrointestinal bleeding was the most frequent identifiable source of PDB in the present study. Interestingly, prior peptic ulcer was relatively more frequent in patients with PDB (8.6 vs. 4.8%, p = .07) with gastric acid inhibitors used rather infrequently after discharge (28.2 vs. 30.8%, p = .55), which might underlie the bleeding. Because proton pump inhibitors significantly reduce gastrointestinal bleeding in patients with selected risk factors,[24] a proton pump inhibitor is recommended to minimize bleeding while on DAPT.[2]

In the present study, significant association was observed between PDB with BARC ≥3 and all-cause mortality. We did not observed the significant association between PDB with BARC ≥2 and all-cause mortality. Therefore, all-cause mortality in the present study might be driven by the PDB with BARC ≥3. However, due to the total number of mortality of events was small in the present study, the results should be further verified. However, further analysis showed that the PDB with BARC ≥2

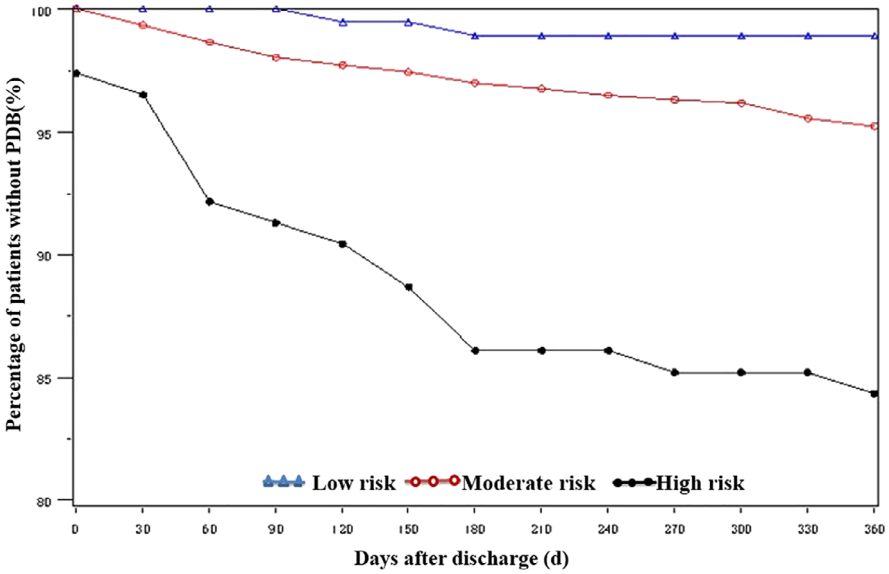


FIGURE 6 Kaplan–Meier estimates of patients free from postdischarge bleeding (PDB) in the overall derivation cohort stratified by score tertiles [Color figure can be viewed at wileyonlinelibrary.com]

was independently associated with higher risk for postdischarge MACE. The relationship between PDB and MACE is likely multifactorial. The risk factors shared between bleeding and ischemic events have explained the higher risk for recurrent ischemic events in patients with bleeding events.[25,26]

Relative to clopidogrel alongside aspirin use, ticagrelor alongside aspirin use was strongly associated with higher risk of PDB with BARC ≥2, but not lower risk of postdischarge MACE. The latter finding is consistent with that in the GRAPE study (the Greek Anti-platelet Registry).[27] Because only a small number of patients on ticagrelor treatment (*n* = 199) were included in the present study, a larger registry study with comparable numbers of ticagrelor and clopidogrel treated patients is warranted to confirm the findings in Chinese patients.

Although multiple scores have been developed to stratify the bleeding risk for ACS or PCI patients, most have focused on short-term events or long-term outcomes which are not directly modified by chronic DAPT use within 1 year in a real world setting.[1,7,13,14,28,29] Therefore, we developed for the first time a risk score for clinically relevant PDB (BARC ≥2) which is most consistently and reproducibly influenced by DAPT.[1,5] For the prediction of PDB with BARC ≥2, the present BRIC-ACS score displayed a relatively moderate discriminative power (*c*-statistics: 0.67) in Chinese ACS patients who underwent PCI. The performance is comparable or relatively better than that of the previous PRECISE-DAPT and PARIS scores, both of which were validated for the prediction of PDB with BARC ≥2 in the CardioCHUVI PCI registry study (*c*-statistics: 0.61 and 0.63, respectively).[30] Moreover, the BRIC-ACS score performed better in patients with NSTEMI, STEMI, diabetes, and those implanted with more than two DESs (*c*-statistics: 0.71–0.80), it might be a useful tool to predict PDB risk in patients with high ischemic and bleeding risk.

Several limitations of the study should be mentioned. First, due to the relatively small sample size (*n* = 2,381) of the present study, the entire cohort was used for the derivation of the BRIC-ACS score. Although no independent validation cohort was established, we validated the BRIC-ACS score with the bootstrap method and in subgroups of patients from the overall cohort. Second, the rate of PDB with BARC ≥3 within 1 year was lower than that reported in other studies,[6,27,31,32] which might be attributed to the inclusion of a high proportion of patients with lower risk of bleeding (e.g., 42.5% of patients with UA). Nonetheless, PDB with BARC ≥3 was independently associated with all-cause mortality and postdischarge MACE within 1 year.[5,33] Third, although we included in the multiple regression analysis as many as possible clinical and procedural risk factors potentially influencing bleeding risk, some might have been omitted. Variables related to bleeding, such as age and creatinine clearance, were absent from the final BRIC-ACS score, indicating that the underlying risk factors or their relative contributions for bleeding are not constant.[34] Fourth, because the recruitment time interval for the study coincided with the beginning of ticagrelor availability in China, the sample size of patients on ticagrelor treatment was small (*n* = 199). Therefore, comparisons of efficacy and safety outcomes between ticagrelor and clopidogrel treated patients should be validated in further studies (such as the ongoing BRIC-ACS stage II registry). Finally, because the established BRIC-ACS bleeding risk score was based specifically on Chinese ACS patients after PCI, validation is warranted in racially diverse populations and non-ACS or PCI patients.

5 | CONCLUSIONS

In conclusion, in a nationwide, multicenter registry study of Chinese ACS patients who underwent PCI, PDB with BARC ≥2 was associated with higher risk for postdischarge MACE. The constructed BRIC-ACS risk score had moderate performance for the discrimination of PDB, which might be useful particularly in patients with high ischemic and bleeding risk.

6 | PERSPECTIVES

6.1 | What is known?

PDB with BARC ≥2 was associated with all-cause mortality in patients underwent PCI. Less known is the impact of PDB on postdischarge MACE.

Moreover, methods to gauge PDB risk in real world settings during the chronic DAPT use phase within 12 months are limited.

6.2 | What the study adds?

PDB with BARC ≥2 is associated with higher risk for postdischarge MACE in Chinese ACS patients who underwent PCI. The constructed BRIC-ACS risk score had moderate performance for the discrimination of PDB, which might be useful particularly in patients with high ischemic and bleeding risk.

6.3 | What is next?

Additional studies are needed to validate the established BRIC-ACS bleeding risk score, which is based on real-world Chinese ACS patients after PCI.

ACKNOWLEDGMENTS

This study was funded by Sanofi. The funder did not participate in study design or execution, drug choice, data analysis, or reporting. The authors would like to thank the investigators and participants for their participation, without whom this study would not have been possible.

ORCID

Yundai Chen https://orcid.org/0000-0003-4409-9375
Shaoping Nie https://orcid.org/0000-0001-9867-3833

REFERENCES

1. Baber U, Mehran R, Giustino G, et al. Coronary thrombosis and major bleeding after pci with drug-eluting stents: risk scores from Paris. J Am Coll Cardiol. 2016;67:2224-2234.
2. Ibanez B, James S, Agewall S, et al. 2017 esc guidelines for the management of acute myocardial infarction in patients presenting with st-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with st-segment elevation of the european society of cardiology (esc). European Heart Journal. 2018;39(2):119–177.
3. Cuisset T, Deharo P, Quilici J, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the topic (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J. 2017;38:3070-3078.
4. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (tropical-acs): a randomised, open-label, multicentre trial. Lancet. 2017;390:1747-1757.
5. Genereux P, Giustino G, Witzenbichler B, et al. Incidence, predictors, and impact of post-discharge bleeding after percutaneous coronary intervention. J Am Coll Cardiol. 2015;66:1036-1045.
6. Kazi DS, Leong TK, Chang TI, Solomon MD, Hlatky MA, Go AS. Association of spontaneous bleeding and myocardial infarction with long-term mortality after percutaneous coronary intervention. J Am Coll Cardiol. 2015;65:1411-1420.
7. Mathews R, Peterson ED, Chen AY, et al. In-hospital major bleeding during st-elevation and non-st-elevation myocardial infarction care: derivation and validation of a model from the action registry(r)-gwtg. Am J Cardiol. 2011;107:1136-1143.
8. Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-st-segment-elevation myocardial infarction: the crusade (can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the acc/aha guidelines) bleeding score. Circulation. 2009;119:1873-1882.
9. Mehran R, Pocock SJ, Nikolsky E, et al. A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol. 2010;55:2556-2566.
10. Rao SV, McCoy LA, Spertus JA, et al. An updated bleeding model to predict the risk of post-procedure bleeding among patients undergoing percutaneous coronary intervention: a report using an expanded bleeding definition from the national cardiovascular data registry cathpci registry. JACC Cardiovasc Interv. 2013;6:897-904.
11. Li S, Liu H, Liu J. Predictive performance of adding platelet reactivity on top of crusade score for 1-year bleeding risk in patients with acute coronary syndrome. J Thromb Thrombolysis. 2016;42:360-368.
12. Valle JA, Shetterly S, Maddox TM, et al. Postdischarge bleeding after percutaneous coronary intervention and subsequent mortality and myocardial infarction: insights from the hmo research network-stent registry. Circ Cardiovasc Interv. 2016;9:e003519.
13. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (precise-dapt) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017;389:1025-1034.
14. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA. 2016;315:1735-1749.
15. Steg PG, Huber K, Andreotti F, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the working group on thrombosis of the European society of cardiology. Eur Heart J. 2011;32:1854-1864.
16. Hamm CW, Bassand JP, Agewall S, et al. Esc guidelines for the management of acute coronary syndromes in patients presenting without persistent st-segment elevation: the task force for the management of Acute Coronary Syndromes (acs) in patients presenting without persistent st-segment elevation of the European Society of Cardiology (esc). Eur Heart J. 2011;32:2999-3054.
17. Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent st-segment elevation: the task force on the management of st-segment elevation acute myocardial infarction of the European society of cardiology. Eur Heart J. 2008;29:2909-2945.
18. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. Circulation. 2011;123:2736-2747.
19. Thygesen K, Alpert JS, White HD, Joint ESCAAHAWHFTFftRoMI. Universal definition of myocardial infarction. Eur Heart J. 2007;28:2525-2538.
20. Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. Clopidogrel in japanese, korean and taiwanese patients with acute coronary syndrome—randomized, double-blind, phase iii philo study. Circ J. 2015;79:2452-2460.

21. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (roc) curve. Radiology. 1982;143:29-36.
22. Genereux P, Cohen DJ, Mack M, et al. Incidence, predictors, and prognostic impact of late bleeding complications after transcatheter aortic valve replacement. J Am Coll Cardiol. 2014;64:2605-2615.
23. Palmerini T, Benedetto U, Bacchi-Reggiani L, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. Lancet. 2015;385:2371-2382.
24. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med. 2010;363:1909-1917.
25. Yadav M, Genereux P, Palmerini T, et al. Syntax score and the risk of stent thrombosis after percutaneous coronary intervention in patients with non-st-segment elevation acute coronary syndromes: an acuity trial substudy. Cathet Cardiovasc Interv. 2015;85:1-10.
26. China Society of Cardiology of Chinese Medical Association, Editorial Board of Chinese Journal of Cardiology. Guideline for diagnosis and treatment of patients with ST-elevation myocardial infarction. Zhonghua Xin Xue Guan Bing Za Zhi. 2010;38:675-690.
27. Alexopoulos D, Xanthopoulou I, Deftereos S, et al. Contemporary antiplatelet treatment in acute coronary syndrome patients undergoing percutaneous coronary intervention: 1-year outcomes from the greek antiplatelet (grape) registry. J Thromb Haemost. 2016;14:1146-1154.
28. Nikolsky E, Mehran R, Dangas G, et al. Development and validation of a prognostic risk score for major bleeding in patients undergoing percutaneous coronary intervention via the femoral approach. Eur Heart J. 2007;28:1936-1945.
29. Montalescot G, Salette G, Steg G, et al. Development and validation of a bleeding risk model for patients undergoing elective percutaneous coronary intervention. Int J Cardiol. 2011;150:79-83.
30. Wright RS, Anderson JL, Adams CD, et al. 2011 ACCF/AHA focused update of the guidelines for the management of patients with unstable angina/non-st-elevation myocardial infarction (updating the 2007 guideline): a report of the american college of cardiology foundation/american heart association task force on practice guidelines developed in collaboration with the american college of emergency physicians, society for cardiovascular angiography and interventions, and society of thoracic surgeons. J Am Coll Cardiol. 2011;57:1920-1959.
31. Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the global registry of acute coronary events (grace). Eur Heart J. 2003;24:1815-1823.
32. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045-1057.
33. Brener SJ, Kirtane AJ, Stuckey TD, et al. The impact of timing of ischemic and hemorrhagic events on mortality after percutaneous coronary intervention: the adapt-des study. JACC Cardiovasc Interv. 2016;9:1450-1457.
34. Li L, Geraghty OC, Mehta Z, Rothwell PM, Oxford Vascular S. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet. 2017;390:490-499.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Chen Y, Yin T, Xi S, et al. A risk score to predict postdischarge bleeding among acute coronary syndrome patients undergoing percutaneous coronary intervention: BRIC-ACS study. *Catheter Cardiovasc Interv*. 2019;1–11. https://doi.org/10.1002/ccd.28325