RESEARCH PAPER

Impact of Antithrombotic Agents on Refining Predictability of In-Hospital Bleeding Events

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Abstract

Objective: To determine whether incorporation of antithrombotic and procedural variables improves prediction of clinically relevant in-hospital bleeding beyond the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) bleeding score in patients with acute myocardial infarction.

Methodology: This prospective single-centre cohort included 400 adults with ST-segment-elevation myocardial infarction (STEMI) or non-ST-segment-elevation myocardial infarction (NSTEMI). Clinically relevant in-hospital bleeding, defined according to the Bleeding Academic Research Consortium (BARC) as type 2 or 3 bleeding, was used as the principal modeling endpoint, while severe in-hospital BARC type 3 or 5 bleeding and post-discharge BARC type 2, 3, or 5 bleeding were analyzed separately. A multivariable logistic regression model incorporated selected clinical, antithrombotic, and procedural variables in addition to the CRUSADE score. Model performance was evaluated using the area under the receiver operating characteristic curve (AUC), calibration, multicollinearity assessment, and 1,000-sample bootstrap internal validation.

Results: Clinically relevant in-hospital BARC type 2 or 3 bleeding occurred in 110 of 400 patients (27.5%), including 28 patients (7.0%) with BARC type 3 bleeding. Among 394 hospital survivors, 54 patients (13.7%) experienced post-discharge BARC type 2, 3, or 5 bleeding through six months. CRUSADE alone demonstrated poor discrimination, with an AUC of 0.535 (95% confidence interval [CI], 0.471–0.601). The extended model achieved an apparent AUC of 0.732 (95% CI, 0.676–0.786), an optimism-corrected AUC of 0.702, and an optimism-corrected Brier score of 0.182. Thrombolysis, ticagrelor 180-mg loading, glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitor use, and number of implanted stents remained independently associated with clinically relevant in-hospital bleeding. In a sensitivity analysis, addition of cardiogenic shock produced minimal change in discrimination (AUC 0.734); its adjusted odds ratio (OR) was 2.65 (95% CI, 0.64–11.04; P=0.181).

Conclusion: CRUSADE alone provided limited discrimination for clinically relevant in-hospital bleeding in this cohort. Incorporation of selected antithrombotic and procedural characteristics improved predictive performance, although discrimination remained moderate after internal validation. These findings support the incremental prognostic value of treatment- and procedure-related variables, but external validation is required before the model can be considered for clinical application.

Keywords: Acute coronary syndrome; BARC bleeding; CRUSADE score; antithrombotic therapy; prediction model.

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Introduction

Management of acute coronary syndrome requires a careful balance between prevention of recurrent ischemic events and avoidance of treatment-related bleeding. Contemporary antithrombotic therapy and invasive reperfusion have substantially improved ischemic outcomes, but hemorrhagic complications remain clinically important because they may necessitate interruption of evidence-based therapy, blood transfusion, prolong hospitalization, and are associated with an adverse prognosis [1]. Current European recommendations therefore support individualized antithrombotic strategies, preferential radial access when feasible, and limitation of unnecessary exposure to therapies associated with increased bleeding risk [2].

Reported bleeding rates vary considerably according to the definition applied. The Bleeding Academic Research Consortium (BARC) classification provides a standardized framework that distinguishes minor bleeding from clinically relevant and major hemorrhagic events. BARC type 2 refers to overt bleeding requiring diagnostic evaluation, hospitalization, or treatment; BARC type 3 encompasses more severe bleeding associated with substantial hemoglobin reduction, transfusion, cardiac tamponade, or intracranial/ocular hemorrhage; and BARC type 5 denotes fatal bleeding [3]. Consistent use of a clearly defined bleeding endpoint is therefore essential when comparing study populations and when developing or validating bleeding-prediction models.

The Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) bleeding score was developed from more than 89,000 patients with non-ST-segment-elevation myocardial infarction and incorporates eight baseline clinical variables to estimate the risk of in-hospital major

bleeding [4]. Although widely used, its discriminatory performance is not uniform across populations and may differ when applied to patients with ST-segment-elevation myocardial infarction, contemporary percutaneous coronary intervention, or treatment pathways that differ from those represented in the original derivation cohort. The Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria provide a complementary framework for identifying patients at increased bleeding risk after percutaneous coronary intervention, but they represent a categorical risk definition rather than an individualized probability model [5].

The present study therefore evaluated whether incorporation of antithrombotic and procedural variables provides incremental predictive information beyond the CRUSADE score in patients admitted with acute myocardial infarction. Clinically relevant in-hospital BARC type 2 or 3 bleeding was evaluated as the principal modeling endpoint, while severe in-hospital bleeding and post-discharge bleeding were analyzed separately. Model performance was assessed using discrimination, calibration, and internal validation.

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Patients and Methods

Study design and population

This prospective, single-centre observational cohort included 400 adults admitted to Maadi Military Hospital with acute myocardial infarction. Eligible participants were aged >18 years, met the Fourth Universal Definition of Myocardial Infarction criteria for STEMI or NSTEMI [6], and provided written informed consent. Patients who declined or withdrew consent, as well as those scheduled for in-hospital coronary artery bypass grafting, were excluded. Clinical data were collected prospectively using a standardized case-report form. The study cohort comprised the 400 eligible patients enrolled in the prospective database, all of whom were included in the in-hospital analyses.

Ethics

The institutional research and ethics committee approved the protocol (MD-6-2021). All participants provided written informed consent. Clinical data were coded and anonymized for analysis, and the study was conducted in accordance with the Declaration of Helsinki.

Clinical assessment and treatment variables

Baseline assessment included demographic characteristics, cardiovascular history, comorbidities, smoking status, pre-admission medication use, physical examination, 12-lead electrocardiography, transthoracic echocardiography, complete blood count, renal function indices, serum electrolytes, coagulation profile, high-sensitivity troponin I, and high-sensitivity C-reactive protein. The CRUSADE score was calculated according to its established components.

Treatment-related variables included thrombolysis; timing and type of P2Y12 inhibitor loading; clopidogrel 300-mg or 600-mg loading; ticagrelor 180-mg loading; pre-procedural anticoagulant category; procedural unfractionated heparin (UFH); GP IIb/IIIa inhibitor use; post-procedural anticoagulation; vascular access; thrombus burden; and number of implanted stents. P2Y12 loading was categorized according to whether it was administered on diagnosis, on admission, or after coronary angiography. Only treatment variables occurring before the bleeding outcome were considered candidate predictors. Therapeutic changes undertaken in response to bleeding, including blood transfusion or interruption of antithrombotic therapy, were not included as predictors of the same event. Exact weight-adjusted anticoagulant doses and detailed procedural characteristics such as sheath size, vascular closure-device use, and operator-level factors were not available for analysis.

Outcomes and follow-up

The principal outcome for the prediction analysis was clinically relevant in-hospital bleeding, defined as BARC type 2 or 3. Severe in-hospital bleeding, defined as BARC type 3 or 5, was evaluated separately. Post-discharge clinically relevant bleeding was defined as BARC type 2, 3, or 5 and was assessed during scheduled clinical follow-up at 60 days and six months.

For the post-discharge analysis, bleeding events were reported cumulatively through six months. When more than one bleeding event occurred during a given assessment period, the highest BARC grade recorded for that patient was used for classification.

Statistical analysis

Categorical variables were expressed as number and percentage and compared using the chi-square test or Fisher exact test, as appropriate. Continuous variables were summarized as median and interquartile range and compared using the Mann–Whitney U test. All tests were two-sided, and $P<0.05$ was considered statistically significant.

For prediction modeling, the base model included the CRUSADE score per 10-point increase. The extended multivariable logistic regression model incorporated CRUSADE score, STEMI presentation, thrombolysis, P2Y12 loading category, GP IIb/IIIa inhibitor use, number of implanted stents, femoral access, and large thrombus burden. Clopidogrel 300 mg was the reference category for P2Y12 loading. Variables were entered simultaneously without stepwise selection and were selected according to clinical relevance and availability before the bleeding event.

Adjusted ORs with 95% CIs and the complete regression equation were reported. Multicollinearity was assessed using variance inflation factors. Model discrimination was evaluated using the AUC, with comparison of the extended model and CRUSADE alone by the DeLong test. Calibration was assessed using a calibration plot, Brier score, Hosmer–Lemeshow goodness-of-fit test, and bootstrap calibration slope. Internal validation was performed using 1,000 bootstrap resamples to estimate optimism-corrected model performance.

Cardiogenic shock was examined in a sensitivity model because of its low frequency. One patient without a valid P2Y12 loading category was excluded from analyses requiring this variable, resulting in a complete-case sample of 399 patients. Statistical analyses were performed using Python 3 with pandas, SciPy, statsmodels, and scikit-learn.

Results

Cohort and bleeding outcomes

The study included 400 patients, of whom 240 (60.0%) presented with STEMI and 160 (40.0%) with NSTEMI. The median age was 56 years, and 230 patients (57.5%) were men. Clinically relevant in-hospital BARC type 2 or 3 bleeding occurred in 110 patients (27.5%), while 54 of 394 hospital survivors experienced post-discharge BARC type 2, 3, or 5 bleeding through six months (Figure 1). Overall, 28 patients (7.0%) experienced severe in-hospital BARC type 3 bleeding, while no BARC type 5 event was recorded. Six patients died during hospitalization. Overall, 136 patients (34.0%) experienced at least one clinically relevant bleeding event during hospitalization or follow-up.

Table 1. Bleeding outcomes during hospitalization and follow-up

Outcome	Patients at risk	Events, n (%)
In-hospital BARC 2 or 3	400	110 (27.5)
In-hospital BARC 2	400	82 (20.5)
In-hospital BARC type 3 bleeding	400	28 (7.0)
In-hospital BARC 5	400	0 (0.0)
Post-discharge BARC type 2, 3, or 5 bleeding through 6 months	394	54 (13.7)
Clinically relevant bleeding during hospitalization or follow-up	400	136 (34.0)

Patients with bleeding in both periods are counted once in the final row. The post-discharge denominator excludes six in-hospital deaths. BARC, Bleeding Academic Research Consortium.

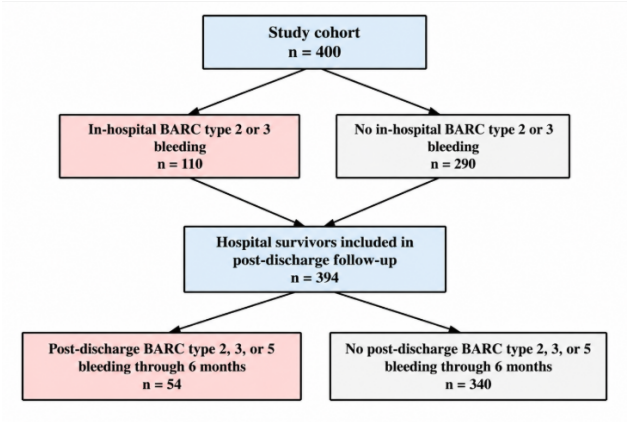


Figure 1. Study cohort and bleeding outcomes during hospitalization and follow-up. Of the 400 enrolled patients, 110 experienced in-hospital BARC type 2 or 3 bleeding. Six patients died during hospitalization; therefore, 394 survivors were included in post-discharge follow-up, of whom 54 experienced BARC type 2, 3, or 5 bleeding through six months. BARC, Bleeding Academic Research Consortium.

Baseline, treatment, and procedural characteristics

Patients with in-hospital BARC type 2 or 3 bleeding had higher frequencies of diabetes mellitus (80.0% vs 69.3%, P=0.033), current smoking (60.9% vs 49.3%, P=0.038), prior acute coronary syndrome (33.6% vs 22.4%, P=0.021), and STEMI presentation (70.9% vs 55.9%, P=0.006) than those without bleeding. Median eGFR was also lower in the bleeding group (87.3 vs 92.6 mL/min/1.73 m², P=0.022). Age, sex, hypertension, renal impairment, right ventricular infarction, baseline hemoglobin, hematocrit, and CRUSADE score did not differ significantly between groups (Table 2).

Table 2. Baseline characteristics according to in-hospital BARC type 2 or 3 bleeding

Variable	BARC 2-3 bleeding (n=110)	No BARC 2-3 bleeding (n=290)	P value
Age, years	56.0 (49.0-64.0)	56.0 (50.0-63.0)	0.516
Male sex	68 (61.8%)	162 (55.9%)	0.282
Diabetes mellitus	88 (80.0%)	201 (69.3%)	0.033
Hypertension	75 (68.2%)	177 (61.0%)	0.186
Renal impairment	14 (12.7%)	23 (7.9%)	0.139
Current smoking	67 (60.9%)	143 (49.3%)	0.038
Prior ACS	37 (33.6%)	65 (22.4%)	0.021
STEMI	78 (70.9%)	162 (55.9%)	0.006
Right ventricular infarction	14 (12.7%)	22 (7.6%)	0.109
Hemoglobin, g/dL	12.0 (11.0-13.0)	12.0 (11.0-13.0)	0.795

Variable	BARC 2-3 bleeding (n=110)	No BARC 2-3 bleeding (n=290)	P value
Hematocrit, %	45.0 (41.0-49.0)	45.0 (40.0-49.0)	0.801
eGFR, mL/min/1.73 m2	87.3 (68.5-101.3)	92.6 (72.9-108.7)	0.022
CRUSADE score	31.0 (21.0-39.8)	29.0 (18.0-38.8)	0.290

Values are presented as median (IQR) or n (%). ACS, acute coronary syndrome; eGFR, estimated glomerular filtration rate.

Thrombolysis (22.7% vs 8.6%, P<0.001), ticagrelor 180-mg loading (29.1% vs 13.4%, P<0.001), GP IIb/IIIa inhibitor use (33.6% vs 16.2%, P<0.001), and large thrombus burden (34.5% vs 17.2%, P<0.001) were more frequent among patients with in-hospital BARC type 2 or 3 bleeding. Clopidogrel 600-mg loading was less frequent in the bleeding group (30.0% vs 46.6%, P<0.001). The median number of implanted stents was higher among patients with bleeding (1.0 [IQR 1.0–2.0] vs 1.0 [IQR 1.0–1.0], P=0.002), whereas femoral access did not differ significantly between groups (63.6% vs 61.7%, P=0.725) (Table 3).

Table 3. Antithrombotic and procedural characteristics according to in-hospital BARC type 2 or 3 bleeding

Variable	BARC 2-3 bleeding (n=110)	No BARC 2-3 bleeding (n=290)	P value
Thrombolysis	25 (22.7%)	25 (8.6%)	<0.001
Ticagrelor 180 mg loading	32 (29.1%)	39 (13.4%)	<0.001
Clopidogrel 600 mg loading	33 (30.0%)	135 (46.6%)	<0.001
GP IIb/IIIa inhibitor	37 (33.6%)	47 (16.2%)	<0.001
Femoral access	70 (63.6%)	179 (61.7%)	0.725
Large thrombus burden	38 (34.5%)	50 (17.2%)	<0.001
Number of stents	1.0 (1.0-2.0)	1.0 (1.0-1.0)	0.002

Values are presented as median (IQR) or n (%). P2Y12 loading was analyzed as a categorical variable, with clopidogrel 300 mg used as the reference category in multivariable analysis.

Prediction model

The principal multivariable analysis included 399 patients and 110 in-hospital BARC type 2 or 3 bleeding events. CRUSADE alone demonstrated poor discrimination, with an AUC of 0.535 (95% CI 0.471–0.601) and a Brier score of 0.199. The extended model improved discrimination to an AUC of 0.732 (95% CI 0.676–0.786), with a Brier score of 0.172. The absolute difference in AUC was 0.197 (DeLong z=5.09, P<0.001).

Following 1,000-sample bootstrap internal validation, the optimism-corrected AUC was 0.702 and the optimism-corrected Brier score was 0.182. The median bootstrap calibration slope was 0.840. The Hosmer–Lemeshow goodness-of-fit statistic was 13.29 (8 df, P=0.102), and the maximum variance inflation factor was 2.53.

In the multivariable model, thrombolysis (adjusted OR 4.36, 95% CI 1.56–12.22; P=0.005), ticagrelor 180-mg loading (adjusted OR 2.74, 95% CI 1.10–6.82; P=0.031), GP IIb/IIIa inhibitor use (adjusted OR 2.47, 95% CI 1.11–5.51; P=0.027), number of stents (adjusted OR 1.45 per additional stent, 95% CI 1.06–1.98; P=0.020), and CRUSADE score (adjusted OR 1.21 per 10-point increase, 95% CI 1.02–1.43; P=0.031) were independently associated with in-hospital BARC type 2 or 3 bleeding. STEMI presentation, clopidogrel 600-mg loading, femoral access, and large thrombus burden were not independently associated with the outcome (Table 4).

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Table 4. Multivariable logistic regression for in-hospital BARC type 2 or 3 bleeding

Predictor	β	Adjusted OR	95% CI	P value
CRUSADE score (per 10 points)	0.188	1.21	1.02–1.43	0.031
STEMI	0.109	1.11	0.53–2.33	0.773
Thrombolysis	1.473	4.36	1.56–12.22	0.005
Clopidogrel 600 mg vs 300 mg	0.058	1.06	0.47–2.38	0.889
Ticagrelor 180 mg vs clopidogrel 300 mg	1.007	2.74	1.10–6.82	0.031
GP IIb/IIIa inhibitor	0.904	2.47	1.11–5.51	0.027
Number of stents (per stent)	0.371	1.45	1.06–1.98	0.020
Femoral access	-0.111	0.89	0.54–1.47	0.662
Large thrombus burden	0.274	1.32	0.59–2.92	0.500

All variables were entered simultaneously into the multivariable logistic regression model. CRUSADE was modeled per 10-point increase. Clopidogrel 300 mg was the reference P2Y12 category.

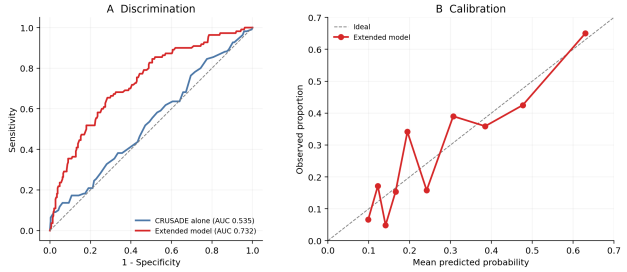


Figure 2. Discrimination and calibration of the bleeding prediction models. (A) Receiver operating characteristic curves for the CRUSADE score alone and the extended multivariable model for prediction of in-hospital BARC

type 2 or 3 bleeding. The AUC was 0.535 for CRUSADE alone and 0.732 for the extended model. (B) Apparent calibration of the extended model across tenths of predicted risk; the dashed line represents ideal agreement between predicted and observed event probabilities. AUC, area under the receiver operating characteristic curve; BARC, Bleeding Academic Research Consortium; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines.

For severe in-hospital BARC type 3 bleeding, the CRUSADE score demonstrated limited discrimination, with an AUC of 0.598 (95% CI 0.470–0.719). For post-discharge BARC type 2, 3, or 5 bleeding through six months, the corresponding AUC was 0.645 (95% CI 0.562–0.730). In a sensitivity analysis, addition of cardiogenic shock to the extended model produced minimal change in discrimination (AUC 0.734); cardiogenic shock was not independently associated with the outcome (OR 2.65, 95% CI 0.64–11.04; P=0.181), and the direction of the remaining model coefficients was unchanged. The discrimination and calibration of the principal model are shown in Figure 2.

In a sensitivity analysis excluding duplicate-pattern observations, model discrimination remained similar, with an AUC of 0.736 for the extended model compared with 0.527 for CRUSADE alone.

Discussion

In this prospective cohort of patients with acute myocardial infarction, clinically relevant in-hospital bleeding occurred in 27.5% of patients, while BARC type 3 bleeding occurred in 7.0%. The principal finding was the limited discriminatory performance of CRUSADE in this population (AUC 0.535). Addition of selected antithrombotic and procedural variables increased the apparent AUC to 0.732, with an optimism-corrected AUC of 0.702 after bootstrap validation. Thrombolysis, ticagrelor 180-mg loading, glycoprotein IIb/IIIa inhibitor use, and the number of implanted stents retained independent predictive information. These results support a dynamic concept of bleeding risk in AMI in which baseline susceptibility is modified by the pharmacological and interventional course.

Clinically relevant bleeding was relatively frequent in the present cohort. Morttada and Shahin [7] reported bleeding in 198 of 823 Egyptian patients with acute coronary syndrome (24.1%), an overall rate close to that observed here. In contrast, Ariza-Solé et al. [8] documented major in-hospital bleeding in 33 of 1,064 STEMI patients undergoing primary PCI (3.1%), whereas Flores-Ríos et al. [9] reported major bleeding in 9.8% of 1,391 STEMI patients. The apparent difference is largely attributable to endpoint definition and clinical setting: the present analysis included BARC type 2 events, which capture overt bleeding requiring medical evaluation or treatment, in addition to BARC type 3 bleeding. Reperfusion strategy, vascular access, case mix, and antithrombotic exposure also differ substantially across cohorts and influence absolute event rates.

The discriminatory performance of CRUSADE was also weaker than that reported in its derivation and several external validations. Subherwal et al. [4] reported C-statistics of approximately 0.70-0.71 in the original CRUSADE cohorts, with a progressive increase in major bleeding across risk categories. Ariza-Solé et al. [8] reported an AUC of approximately 0.80 in STEMI patients undergoing primary PCI, and Flores-Ríos et al. [9] found a C-statistic of 0.77. Jinatongthai et al. [10] likewise demonstrated useful discrimination in ACS patients receiving enoxaparin. The AUC of 0.535 in the present study therefore indicates poor transportability of CRUSADE to this particular population rather than absence of baseline bleeding risk. Sixty percent of the cohort had STEMI, 72.2% had diabetes, and contemporary reperfusion and antithrombotic strategies introduced risk components that are not represented in a score derived predominantly from an earlier NSTE-ACS population.

The incremental information provided by treatment variables is consistent with contemporary observations that bleeding risk continues to evolve after admission. Sun et al. [11] showed that in-hospital major bleeding in ACS was related to both clinical characteristics and treatment exposure and was associated with an adverse prognosis. In the present cohort, thrombolysis showed the strongest independent association with clinically relevant bleeding (adjusted OR 4.36, 95% CI 1.56-12.22). Systemic fibrinolysis, concomitant antiplatelet and anticoagulant therapy, and subsequent rescue or pharmacoinvasive PCI provide a plausible clinical basis for this association. Because reperfusion strategy was not randomized, however, the coefficient should be regarded as predictive rather than as a causal estimate of the effect of fibrinolysis.

Glycoprotein IIb/IIIa inhibitor use was independently associated with bleeding (adjusted OR 2.47, 95% CI 1.11-5.51). Morttada and Shahin [7] similarly reported a markedly higher frequency of bleeding among patients exposed to GP IIb/IIIa antagonists. Current ACS recommendations restrict routine use of these agents and favor selective bailout administration for no-reflow or acute thrombotic complications [1,2]. In that setting, the observed association probably reflects both the potent antiplatelet effect of GP IIb/IIIa inhibition and the greater thrombotic and procedural complexity of patients in whom it is required.

Ticagrelor 180-mg loading also retained an independent association with the bleeding endpoint (adjusted OR 2.74, 95% CI 1.10-6.82), whereas clopidogrel 600-mg loading was no longer associated with bleeding after multivariable adjustment. This pattern is compatible with treatment-selection effects in routine ACS practice, where P2Y12 inhibitor choice is influenced by ischemic presentation, age, renal function, previous antiplatelet exposure, invasive strategy, and perceived hemorrhagic risk. Randomized evidence confirms that the intensity and duration of antiplatelet treatment materially affect bleeding after PCI. Valgimigli et al. [12], in MASTER DAPT, showed that abbreviated dual antiplatelet therapy reduced major or clinically relevant nonmajor bleeding in high-bleeding-risk patients. Escaned et al. [13] similarly reported lower

BARC type 2, 3, or 5 bleeding with ticagrelor monotherapy after early aspirin withdrawal in the TWILIGHT-HBR analysis. These trials address treatment strategies rather than the present loading-dose comparison, but they reinforce the importance of cumulative antithrombotic exposure.

Procedural complexity also contributed to risk stratification. Each additional implanted stent was associated with a 45% increase in the adjusted odds of clinically relevant bleeding (OR 1.45, 95% CI 1.06-1.98). Stent number is more plausibly interpreted as a marker of extensive coronary disease and procedural burden than as an isolated hemorrhagic determinant, because multistent PCI often entails longer procedures, greater vessel instrumentation, and more intensive adjunctive therapy. Large thrombus burden was associated with bleeding in unadjusted analysis but lost significance after multivariable adjustment, suggesting that part of its effect was captured by treatment intensity and procedural complexity. Femoral access was not independently associated with bleeding; this finding should not be interpreted as equivalence between access strategies because access was not randomized and detailed sheath, closure-device, and puncture-site data were unavailable. Contemporary evidence and guidelines continue to favor radial access in ACS because of lower access-site bleeding and vascular complications [1,2].

Baseline vulnerability nevertheless remained clinically important. eGFR was lower among patients who bled, while the CRUSADE term became independently associated with the endpoint after treatment and procedural variables were incorporated (OR 1.21 per 10-point increase). Renal function was not entered separately because creatinine clearance is already embedded within CRUSADE and simultaneous inclusion would duplicate prognostic information. The importance of renal impairment, anemia, age, and other baseline determinants is also reflected in the ARC-HBR framework [5]. Abu-Assi et al. [14] demonstrated the applicability of ARC-HBR among ACS patients undergoing PCI, while Ueki et al. [15] validated the criteria in 12,121 PCI patients, in whom BARC type 3 or 5 bleeding occurred in 6.4% of HBR patients versus 1.9% of non-HBR patients. Choi et al. [16] further showed that ARC-HBR and PRECISE-DAPT provided comparable discrimination for 1-year bleeding after PCI.

Large contemporary validation datasets provide a useful benchmark for the degree of discrimination expected from static bleeding-risk tools. Cao et al. [17] evaluated 9,623 patients undergoing coronary stenting and found 1-year bleeding in 9.1% of HBR versus 3.2% of non-HBR patients, with a stepwise increase as multiple ARC-HBR criteria accumulated. In a systematic review and meta-analysis of 68,874 PCI patients, Montalto et al. [18] found a 2.70-fold higher risk of major bleeding among ARC-HBR patients, but pooled discrimination remained moderate (C-statistic 0.69). These findings are relevant to the present model because they show that clinically useful risk gradients do not necessarily translate into high individual-level discrimination and provide a rationale for evaluating additional treatment-related information.

Clinical presentation itself may further modify bleeding risk. Gragnano et al. [19], analyzing 16,821 PCI patients, found higher 1-year BARC type 3 or 5 bleeding after ACS than chronic coronary syndrome (4.97% vs 3.60%) and lower ARC-HBR discrimination in the ACS subgroup. Yoshioka et al. [20] identified low serum albumin as an independent correlate of bleeding after primary PCI for AMI, illustrating that systemic vulnerability may extend beyond variables included in conventional scores. Together, these data support the broader interpretation that bleeding risk in AMI is multidimensional and changes as clinical severity, systemic condition, and treatment exposure evolve.

Cardiogenic shock was examined because it may amplify bleeding through hemodynamic instability, renal hypoperfusion, invasive support, and treatment escalation. Only nine patients in the present cohort had shock, limiting precision. Addition of shock to the full model yielded an adjusted OR of 2.65 (95% CI 0.64-11.04) and changed the AUC only from 0.732 to 0.734. The wide confidence interval is therefore more informative than the nonsignificant P value and indicates that the dataset was insufficient to quantify the independent contribution of this infrequent exposure reliably.

The extended model improved apparent discrimination over CRUSADE by 0.197 AUC units, but bootstrap validation reduced the AUC from 0.732 to 0.702 and yielded a calibration slope of 0.840; the optimism-corrected Brier score was 0.182. This attenuation indicates some overfitting but also shows persistence of incremental predictive information after internal validation. Pufulete et al. [21], using population-based data from ACS patients undergoing PCI, likewise demonstrated clinically meaningful variation in bleeding according to antiplatelet regimen, reinforcing the relevance of treatment exposure when estimating hemorrhagic risk in contemporary practice.

The model should therefore be regarded as exploratory rather than as a replacement for CRUSADE or ARC-HBR. Collins et al. [22] emphasized that prediction-model reporting should include the complete model, discrimination, calibration, and validation rather than ROC performance alone. Riley et al. [23] further showed that model-development sample size should consider outcome frequency, predictor parameters, anticipated model fit, and calibration precision rather than depend solely on a fixed events-per-variable rule. Consistent with PROBAST principles described by Wolff et al. [24], external validation remains necessary before the equation can be considered sufficiently robust for clinical decision-making.

The clinical implication is that bleeding-risk assessment in AMI may be more informative when approached dynamically. Baseline susceptibility - reflected by renal function, anemia, hemodynamic status, diabetes, and established bleeding-risk tools - defines the initial risk profile, while reperfusion strategy, potency of antithrombotic therapy, vascular access, thrombotic burden, and procedural complexity modify that risk during hospitalization. This framework may explain why patients with similar admission risk profiles develop substantially

different hemorrhagic outcomes once their treatment pathways diverge.

Strengths and limitations

The study has several strengths. Data were collected prospectively in a defined cohort of patients with acute myocardial infarction, and in-hospital and post-discharge bleeding outcomes were analyzed separately. The prediction analysis incorporated clinically relevant treatment and procedural variables, reported the complete regression equation, formally compared discrimination with the CRUSADE score, assessed calibration and multicollinearity, and used bootstrap internal validation. Additional sensitivity analyses evaluating cardiogenic shock and data-pattern robustness showed little change in overall model performance.

Several limitations should be acknowledged. This was a single-centre observational study, and antithrombotic and procedural strategies were determined clinically rather than randomly; residual confounding by indication therefore remains possible. The principal modeling endpoint included BARC type 2 or 3 bleeding, while severe BARC type 3 or 5 bleeding was analyzed separately. Detailed information on exact patient-level anticoagulant dosing, GP IIb/IIIa infusion duration, sheath size, vascular closure devices, and operator-level characteristics was unavailable for inclusion in the model. Independent blinded adjudication of bleeding events was not documented, and no formal a priori sample-size calculation was performed. In addition, detailed screening and recruitment-flow information before enrollment was unavailable. Although sensitivity analyses supported the stability of the principal discrimination estimates, external validation in an independent cohort is required before the model can be considered for clinical use.

Conclusion

The CRUSADE score alone showed limited discrimination for clinically relevant in-hospital bleeding in this cohort. Incorporation of selected antithrombotic and procedural variables improved predictive performance, with an optimism-corrected AUC of 0.702 after internal validation. Thrombolysis, ticagrelor loading, GP IIb/IIIa inhibitor use, and number of implanted stents provided independent predictive information beyond CRUSADE. These associations should be interpreted within the observational design and should not be considered causal treatment effects. External validation and, where necessary, recalibration is required before the model can be applied in routine clinical risk stratification.

Declarations

Ethics approval: Institutional research and ethics committee approval MD-6-2021; written informed consent was obtained from all participants.

Funding: No external funding was reported in the submitted study materials.

Conflict of interest: No conflict of interest was reported in the submitted study materials.

Data availability: De-identified patient-level data are retained by the study team; access is subject to institutional and ethical approval.

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