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## Original Article

# CRUSADE bleeding score as a predictor of bleeding events in patients with acute coronary syndrome in Zagazig University Hospital



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## ABSTRACT

**Aim:** To examine the value of CRUSADE bleeding score in predicting bleeding events in our local patients with acute coronary syndrome (ACS) in Zagazig University Hospitals.

**Methods:** Our study included 240 patients with ACS. They underwent history and clinical examination; 12-lead electrocardiography; echocardiography; troponin I, hematocrit value; estimated glomerular filtration rate (eGFR); application of CRUSADE score; and follow-up of the hospital stay and documentations of events. Patients were classified into two groups: Group I: patients with major bleeding, and Group II: patients without major bleeding.

**Results:** Patients with major bleeding were significantly older, with more diabetic and hypertensive patients, more prior vascular disease, heart failure, and less patients with unstable angina, higher heart rate and systolic blood, lower eGFR, and higher CRUSADE risk score.

CRUSADE bleeding score was the strongest predictor of major bleeding. Sensitivity of CRUSADE score  $\geq 33$  in prediction of major bleeding in the whole study group was 80%, specificity was 73.4%, positive predictive value was 26.9%, negative predictive value was 96.9%, overall accuracy was 74.1%. Sensitivity of CRUSADE score  $\geq 38.5$  in prediction of major bleeding in the STEMI patients was 70%, specificity was 84.8%, positive predictive value was 50%, negative predictive value was 92.9%, and overall accuracy was 82.1%.

**Conclusion:** CRUSADE score is a good predictor for major bleeding in Egyptian patients with ACS. It is applicable in UA/NSTEMI as well as in STEMI patients and in women as well as in men.

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## 1. Introduction

Coronary artery disease (CAD) is one of the most important leading causes of death in the whole world.<sup>1</sup> Among the

different clinical presentations of CAD, acute coronary syndrome (ACS) is the most important and life threatening condition.<sup>2</sup>

Different pathogeneses may share in the development of ACS. However, thrombosis is one of the most important.<sup>3</sup>

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Therefore, antithrombotic therapies represent a cornerstone in the management of patients with ACS.<sup>4</sup>

In spite of their obvious effect, antithrombotic therapies for ACS significantly increase bleeding.<sup>5</sup> Hence, it is important to predict the bleeding risk in ACS patients in order to modify their treatment aiming to reduce their bleeding events and improve their outcome.

Various bleeding risk scores were developed and tested. Among those, CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) is very significant. Bleeding score was found to be the most accurate in the prediction of major bleeding events.<sup>6</sup> However, these models have not been evaluated for Egyptian situation with different patients' characteristics and treatment patterns.

The aim of the current study was to examine the value of CRUSADE bleeding score in predicting the bleeding events in our local patients with ACS in Zagazig University Hospitals.

## 2. Methods

Our study took place in Zagazig University Hospitals during the period from September 2014 to October 2015. Our study included 240 patients with ACS (145 males and 95 females). Their age ranged from 41 to 77 years with mean age of  $58.1 \pm 10.48$  years. Patients were included in our study if they fulfilled at least two of the following criteria:

- Presence of typical, chest pain, which is defined as retro-sternal oppressive or compressive, which occurs at rest or with minimal exertion lasting for at least 10 min.<sup>7</sup>
- Electrocardiographic changes in the form of ST-depression, ST-elevation, or new T-wave inversion.
- Positive cardiac enzymes according to the third universal definition of myocardial infarction.<sup>8</sup>

If there were persistent ST-segment elevation  $\geq 1$  mm in at least two contiguous leads, reciprocal ST-segment depression  $\geq 1$  mm in  $V_1$  or  $V_2$ , or presumed new left bundle branch block;

then patients were considered as having ST-segment Elevation Myocardial Infarction (STEMI).<sup>8</sup> If cardiac biomarkers were elevated without any of the previous ECG changes; then patients were considered as having Non-ST-segment Elevation Myocardial Infarction (NSTEMI).<sup>9</sup> Otherwise, patients were considered as having Unstable Angina (UA).

Patient on oral anticoagulation and patient, who died or discharged within 48 h of admission were excluded from our study.

After giving an informed written consent, all patients were subjected to the following:

- 1) Full history taking and thorough clinical examination
- 2) Complete 12-leads electrocardiography
- 3) Echocardiography: Echocardiographic studies were performed for all patients using Philips IE33 and GE VIVID E9 machines with 2.5 MHz transducers. The left ventricular ejection fraction (LVEF) was measured using the modified Simpson's method from the 2-dimensional apical 4-chamber view.<sup>10</sup>

### 4) Laboratory testing

The following laboratory tests were conducted on all patients:

- Cardiac troponin I level: at presentation and 6 h after symptoms onset.<sup>4</sup>
- Hematocrit level: at admission, at discharge, and when there is any sign of bleeding.
- Estimated glomerular filtration rate (eGFR) calculation: eGFR was calculated according to the Cockcroft–Gault formula.<sup>11</sup>

### 5) Application of CRUSADE bleeding risk score according to the data seen in Table 1.<sup>12</sup>

### 6) Treatment of patients

All NSTEMI and UA angina patients were treated according to the ischemia-guided strategy.<sup>4</sup> All patients received double antiplatelet therapy (aspirin and clopidogrel) and enoxaparin according to the 2014 guidelines of AHA/ACC for the management of UA/NSTEMI.

All STEMI patients received thrombolytic therapy with streptokinase in addition to double antiplatelet (aspirin and

**Table 1 – Application of CRUSADE bleeding score.**

Peridictor	Range	Score	Predictor	Range	Score
Baseline hematocrit	<31	9	Systolic blood pressure	91–100	8
	31–33.9	7		101–120	5
	34–36.9	3		121–180	1
	37–39.9	2		181–200	3
Creatinine clearance	>15–30	35	Heart rate	$\geq 201$	5
	>30–60	28		71–80	1
	>60–90	17		81–90	3
	>90–120	7		91–100	6
	>120	0		101–110	8
Diabetes mellitus	No	0	Prior vascular disease	111–120	10
	Yes	6		$\geq 121$	11
Signs of heart failure	No	0	Female sex	No	0
	Yes	7		Yes	8

**Table 2 – Population characteristics and clinical data.**

	Major bleeding (n = 26)	No major bleeding (n = 214)	p
Age (years)	65.1 ± 5.51	57.3 ± 10.64	<0.00001
Sex			
Male	14 (53.8%)	131 (61.2%)	0.468
Female	12 (42.2%)	83 (38.8%)	
Weight (kg)	78.7 ± 10.94	82.3 ± 14.36	0.128
Diabetes	23 (88.5%)	60 (28%)	<0.00001
Hypertension	18 (69.2%)	57 (26.4%)	<0.00001
Smoking	3 (11.5%)	44 (20.6%)	0.274
Dyslipidemia	7 (26.9%)	33 (15.4%)	0.137
Prior vascular disease	19 (73.1%)	44 (20.6%)	<0.00001
Prior myocardial infarction	6 (23.1%)	41 (19.2%)	0.635
Prior coronary revascularization	3 (11.5%)	53 (24.8%)	0.132
Heart failure on admission	12 (46.2%)	45 (21%)	0.004
ACS type			
-UA	4 (15.4%)	88 (41.1%)	0.011
-NSTEMI	12 (46.2%)	80 (37.4%)	0.366
-STEMI	10 (38.4%)	46 (21.5%)	0.055
Heart rate (beat/min)	100.1 ± 22.55	88 ± 15.8	0.0084
Systolic blood pressure (mmHg)	150.8 ± 21.52	127.1 ± 25.78	<0.00001
Baseline hematocrit (%)	3.9 ± 6.12	40.3 ± 4.35	0.259
eGFR (ml/min)	66.5 ± 30.02	96.7 ± 32.37	<0.00001
CRUSADE score	44.7 ± 11.67	28.3 ± 11.93	<0.00001
CRUSADE score ≥33	18 (69.2%)	61 (28.5%)	<0.00001
Ejection fraction (%)	57.2 ± 8.61	62.1 ± 9.31	0.0071

clopidogrel) and enoxaparin according to the 2013 guidelines of ACCF/AHA for the management of STEMI.<sup>13</sup>

#### 7) Follow-up and documentations of in-hospital events

The patients were followed up during their hospital stay, and the following in-hospital events were documented:

- Mortality.
- In-hospital heart failure.
- Cardiogenic shock.
- Coronary revascularization; with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).
- Major bleeding: the following bleeding events were considered as major bleeding: intracranial bleeding, documented retroperitoneal bleeding, a fall in hematocrit of 12% from baseline, or any red blood cell transfusion in which baseline hematocrit was ≥28% or <28% with clinically documented bleeding. In patients, who underwent surgical revascularization, only major bleeding events that occurred before the intervention were taken into account.<sup>12</sup>

According to the presence or the absence of major bleeding, patients were classified into two groups:

**Group I:** Patients with major bleeding (26 patients, 14 males and 12 females, their mean age was 65.1 ± 5.51 years).

**Group II:** Patients without major bleeding (214 patients, 131 males and 83 females, their mean age was 57.3 ± 10.64 years).

All data were analyzed using the SPSS 19 package program (SPSS, Chicago, IL, USA). Differences among the study groups were analyzed by Student's t-test and  $\chi^2$ -test. The correlations among different variables were investigated by Pearson correlation analysis areas under the ROC curve for clinical event models were compared using MedCalc version 11.6.1

(MedCalc Software, Mariakerke, Belgium). A p value <0.05 was regarded as being statistically significant.

The study protocol had been approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University.

### 3. Results

As shown in Table 2, there was no significant difference between the study groups concerning sex, weight, smoking, dyslipidemia, prior myocardial infarction, prior coronary revascularization, or baseline hematocrit value.

Patients with major bleeding were significantly older than patients without major bleeding ( $p < 0.00001$ ). There were significantly more diabetic, more hypertensive, and more patients with prior vascular disease among major bleeding group ( $p < 0.00001$  for each). Prior vascular disease was defined according to the CRUSADE registry (prior stroke and/or peripheral artery disease).<sup>12</sup>

On hospital admission, there were significantly more patients in heart failure among major bleeding group ( $p < 0.00001$ ).

Regarding the type of ACS, there were significantly less patients presented with UA among major bleeding group ( $p = 0.011$ ).

At presentation, patients with major bleeding had significantly higher heart rate ( $p = 0.0084$ ) and systolic blood pressure ( $p < 0.00001$ ).

The eGFR was significantly lower in patients with major bleeding than ( $p < 0.00001$ ). Also, LVEF was significantly lower in ( $p = 0.0071$ ).

The CRUSADE score was significantly higher in patients with major bleeding ( $p < 0.00001$ ). Also, there were more

**Table 3 – In-hospital events and outcome.**

	Major bleeding (n = 26)	No major bleeding (n = 214)	p
Death	1 (3.8%)	10 (4.7%)	0.849
In-hospital heart failure	8 (30.8%)	27 (12.6%)	0.013
Cardiogenic shock	2 (7.7%)	10 (4.7%)	0.505
PCI	13 (42.3%)	62 (29%)	0.029
CABG	2 (7.7%)	9 (4.2%)	0.442

**Table 4 – Regression analysis.**

Variables	Score	Degree of freedom	p
CRUSADE score	37.48	1	<0.00001
Diabetes mellitus	37.415	1	<0.00001
Prior vascular disease	33.027	1	<0.00001
Basal hematocrit	20.078	1	<0.00001
Hypertension	19.578	1	<0.00001
eGFR	18.977	1	<0.00001
Systolic blood pressure	18.733	1	0.00034
Age	12.934	1	0.00052
Heart rate	11.71	1	0.0015
Heart failure during hospital	6.133	1	0.013
Heart failure at admission	0.162	1	0.687

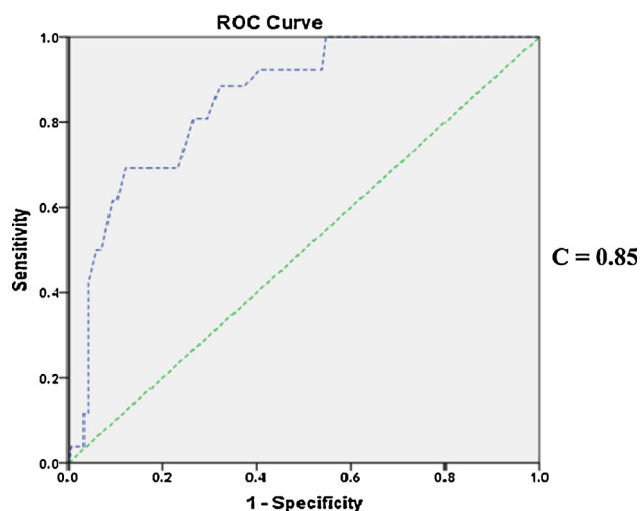
patients with CRUSADE score  $\geq 33$  among patients with major bleeding ( $p < 0.00001$ ).

Regarding in-hospital outcome, as shown in Table 3, there was no significant difference between the two groups regarding death, developing cardiogenic shock, or doing CABG.

In patients with major bleeding, more patients developed heart failure during hospital stay ( $p = 0.013$ ). Also, more patients had undergone PCI during hospital stay ( $p = 0.029$ ).

Regression analysis of the relation of different parameters to the development of major bleeding is shown in Table 4. CRUSADE bleeding score was the strongest independent predictor of major bleeding ( $p < 0.00001$ ). Other significant independent predictors were in order of significance: diabetes mellitus, prior vascular disease, basal hematocrit, hypertension, eGFR ( $p < 0.00001$  for each), systolic blood pressure ( $p = 0.00034$ ), age ( $p = 0.00052$ ), heart rate ( $p = 0.0015$ ), and heart failure during hospital stay ( $p = 0.013$ ).

The validity of CRUSADE score  $\geq 33$  in prediction of major bleeding in the whole study group is shown in Table 5. Sensitivity of was 80%, specificity was 73.4%, positive predictive value was 26.9%, negative predictive value was 96.9%, and overall accuracy was 74.1%,  $p = 0.0013$ . The receiver operating



**Fig. 1 – ROC curve for CRUSADE score with major bleeding events in total population.**

characteristic (ROC) curve analysis is shown in Fig. 1, and area under ROC-curve is 0.85.

The validity of CRUSADE score  $\geq 38.5$  in prediction of major bleeding among STEMI patients is shown in Table 6. Sensitivity of was 70%, specificity was 84.8%, positive predictive value was 50%, negative predictive value was 92.9%, and overall accuracy was 82.1%,  $p = 0.00021$ . The ROC curve analysis is shown in Fig. 2, and area under ROC-curve was 0.79.

The validity of CRUSADE score  $\geq 36$  in prediction of major bleeding among women is shown in Table 7. Sensitivity of was 66.7%, specificity was 89.2%, positive predictive value was 47.1%, negative predictive value was 94.9%, and overall accuracy was 86.3%,  $p = 0.00008$ . The ROC curve analysis is shown in Fig. 3, area under ROC-curve was 0.89.

The rates of major bleeding in different CRUSADE score groups are shown in Table 8. The rate of bleeding was 3.4% in patients with very low risk (score  $\leq 20$ ), 5.6% in patients with low risk (score 21–30), 12.1% in patients with moderate risk (score 31–40), 25.8% in patients with high risk (score 41–50), and was 35.3% in patients with very high risk (score  $> 50$ ).

#### 4. Discussion

Hemorrhagic complications are the most common non-ischemic complications encountered in patients with ACS. The frequency of major hemorrhaging oscillates between 2%

**Table 5 – Validity of CRUSADE score in prediction of major bleeding in all patients.**

	Major bleeding		No major bleeding		Total	
CRUSADE < 33	5		157		162	
CRUSADE $\geq 33$	21		57		78	
Total	26		214		240	
Sensitivity	Specificity	PPP	NPV	Overall accuracy	Kappa	p
80%	73.4%	26.9%	96.9%	74.1%	0.28	0.0013

PPV, positive predictive value; NPV, negative predictive value.

**Table 6 – Validity of CRUSADE score in prediction of major bleeding in STEMI patients.**

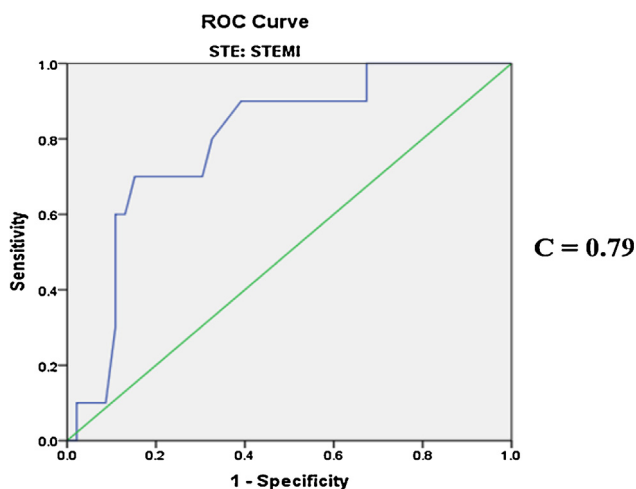
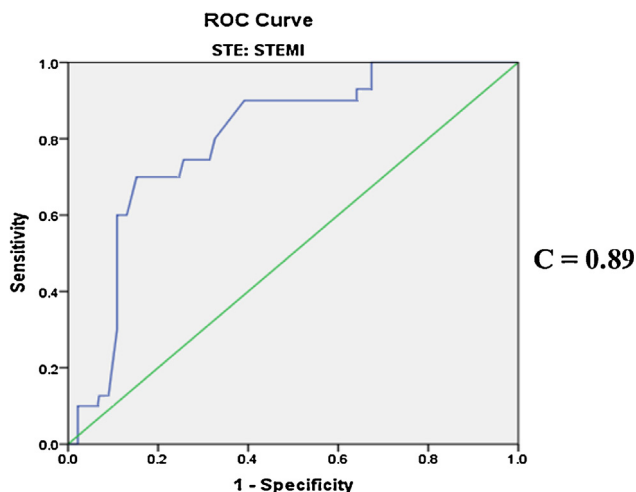
	Major bleeding		No major bleeding		Total	
CRUSADE < 38.5	3		39		42	
CRUSADE ≥ 38.5	7		7		14	
Total	10		46		56	
Sensitivity	Specificity	PPP	NPV	Overall accuracy	Kappa	p
70%	84.8%	50%	92.9%	82.1%	0.47	0.00021

PPV, positive predictive value; NPV, negative predictive value.

**Table 7 – Validity of CRUSADE score in prediction of major bleeding in women.**

	Major bleeding		No major bleeding		Total	
CRUSADE < 36	4		74		78	
CRUSADE ≥ 36	8		9		17	
Total	12		83		95	
Sensitivity	Specificity	PPP	NPV	Overall accuracy	Kappa	p
66.7%	89.2%	47.1%	94.9%	86.3%	0.53	0.00008

PPV, positive predictive value; NPV, negative predictive value.

**Fig. 2 – ROC curve for CRUSADE score with major bleeding events in STEMI population.****Fig. 3 – ROC curve for CRUSADE score with major bleeding events in women.**

and 9% across the spectrum of ACS without ST-segment elevation, largely depending on the definition and the type of treatment used, particularly the dose of antithrombotic agents prescribed and the invasive procedures undertaken.<sup>14</sup>

The present study was done to test the validity of the CRUSADE bleeding risk model in the prediction of major bleeding in Egyptian patients with ACS, either UA/NSTEMI or STEMI.

Although the CRUSADE score was developed by using the database of patients with high-risk non-ST-elevation ACSs admitted in American hospitals, of whom only less than 1% were of Middle Eastern origins,<sup>15</sup> our results showed that the validity of the CRUSADE bleeding risk model in Egyptian patients with ACS was more or less satisfactory, either in patients with UA/NSTEMI or STEMI.

Several published studies demonstrated successful use of CRUSADE score in the prediction of major bleeding in different populations with ACS from various Western countries. Abu-Assi et al. evaluated the validity of the CRUSADE bleeding risk score in a cohort of 782 hospitalized patients with UA/NSTEMI in a Spanish population. They have found that The CRUSADE risk score was generally validated and found to be useful in the Spanish cohort of patients treated with or without multiple antithrombotic therapy either they underwent cardiac catheterization or not.<sup>16</sup>

Also, Kharchenko and his colleagues had studied the prognostic value of CRUSADE bleeding risk score in 602 patients

**Table 8 – CRUSADE score groups and major bleeding.**

CRUSADE risk	Total number	Major bleeding
Very low (≤20)	56	2 (3.4%)
Low (21–30)	85	5 (5.6%)
Moderate (31–40)	39	5 (12.1%)
High (41–50)	23	8 (25.8%)
Very high (>50)	11	6 (35.3%)



with UA/NSTEMI, who were admitted to a Moscow community noninvasive hospital. They found sensitivity and specificity of the CRUSADE score for major and moderate bleedings during hospitalization were 77% and 52%, respectively; with area under ROC-curve was 0.68.<sup>17</sup>

Boden et al. had studied the risk of in-hospital major CRUSADE bleeding and 1-year mortality after primary PCI for 965 Dutch STEMI patients, who received abciximab, periprocedural heparin and loading doses of aspirin and clopidogrel. They had found that major bleeding was common after primary PCI for STEMI and associated with increased mortality during 1-year follow-up. However, they found that the CRUSADE bleeding risk score had underestimated the risk of major bleeding, and they concluded that the use of this score might be limited in STEMI patients.<sup>18</sup>

The CRUSADE bleeding risk score has been evaluated not only in North America and Western Europe, but also in the Far East. Jinatongthai et al. had studied the validity of CRUSADE score in predicting major bleeding in Thai patients with ACS receiving enoxaparin. They had found that the CRUSADE model demonstrated a satisfactory discriminatory capacity for the entire study population (C = 0.688), UA (C = 0.591), NSTEMI (C = 0.693), and STEMI groups (C = 0.736). They concluded that CRUSADE risk score was able to estimate in-hospital major bleeding of Thai patients with ACS, who received treatment with enoxaparin.<sup>19</sup>

The wide applicability of CRUSADE risk score in an extensive range of population may be explained by many reasons. The score was developed from a very large patient registry from a real-life practice, so its variables were widely applicable in many different situations. Many variables in CRUSADE, such as female gender, low baseline hematocrit, and presence of organ failure such as heart or kidney failure were commonly identified and used by other bleeding risk models.<sup>20,21</sup>

Although we have found that CRUSADE risk score was a good predictor of major bleeding in the whole group and in STEMI subgroup, however, we did not find significant difference between patients with and without major bleeding regarding hospital mortality. This result was discordant to the results found by Amador et al., as they found a strong relation between major bleeding and hospital mortality. They also found that CRUSADE bleeding risk score was as valid as ischemia risk score like TIMI and GRACE risk scores in predicting mortality.<sup>22</sup>

The rates of bleeding in our study were higher than those found by the original CRUSADE investigators.<sup>12</sup> These differences were much obvious among patients with high risk (25.8% in our results versus 11.9% in CRUSADE), and among patients with very high risk (35.3% in our results versus 19.5% in CRUSADE). These differences may be explained by the center, where the study was done, Zagazig University Hospital, which is a tertiary hospital to which patients with more severe diseases and co-morbidities are referred. Other possible explanation is the endemic diseases that are more common in Egypt and may affect the coagulation profile like hepatitis C virus (HCV), as the highest prevalence of HCV infection around the world was found to be in Egypt (15–20%), while its global prevalence was found to be 2.2%.<sup>23</sup>

## 5. Conclusion

- CRUSADE bleeding risk score is a good predictor for major bleeding among Egyptian patients with ACS.
- Application of CRUSADE bleeding risk score may be helpful in Egypt.
- The risk was found to be applicable in UA/NSTEMI as well as in STEMI patients, and in women as well as in men.

## Study limitations

- Relatively small number of patients.
- The study was done in a single center.

## Conflicts of interest

The authors have none to declare.

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