Use of Crusade Risk Score in predicting major bleeding among acute myocardial infarction patients receiving Streptokinase

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Abstract

Introduction: Thrombolysis therapy in the management of acute myocardial infarction (AMI) significantly increases major bleeding risk. As major bleeding is associated with mortality, predicting the bleeding could improve the overall outcome of thrombolysis therapy. The use of CRUSADE risk score has not been evaluated among the Malaysian population, particularly in AMI patients who received streptokinase.
Objective: This study aimed to evaluate the association of the patient characteristics and clinical outcomes with major bleeding events and to examine the prognostic value of CRUSADE risk score in predicting major bleeding among AMI patients in Hospital Selayang.
Method: AMI patients admitted to Hospital Selayang who received streptokinase from Jan 2015 to Dec 2018 were included through universal sampling. Patients were grouped into major bleeding and non-major bleeding groups. Patients' demographic data, baseline clinical characteristics and clinical outcomes during the hospital stay were extracted from the electronic medical records. The CRUSADE risk score was calculated for all patients and tested using C statistic and receiver operating characteristics (ROC) curve.
Results: In this study, 143 AMI patients with median age of 54 years old (interquartile range (IQR) 14) were included. Three patients had major bleeding (2.1%), while 31 patients had minor bleeding (21.7%). Patients with minor bleeding and without bleeding were grouped into the non-major bleeding group (n=140, 97.1%). There was no significant differences in the demographics and baseline characteristics between the two groups. Major bleeding was associated with mortality (p=0.013) and longer duration of hospital stay (p=0.003). There was no significant prognostic value of the CRUSADE model in predicting major bleeding among AMI patients receiving Streptokinase [C=0.539; 95% Confidence Interval (CI) 0.353-0.726; p=0.816].
Conclusion: CRUSADE risk score was not an independence predictor of major bleeding in AMI patients who received streptokinase in Hospital Selayang. Future study with a larger population is needed to get more significant results.
Keywords: Acute myocardial infarction, CRUSADE risk score, thrombolysis therapy, major bleeding

NMRR ID: NMRR-16-1817-32350

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Introduction

The leading cause of morbidity and mortality worldwide and in Malaysia is coronary artery disease (1–4). According to the World Health Organization (WHO), 115.14 deaths per 100,000 population in Malaysia in 2019 were caused by coronary artery disease, which includes acute coronary syndrome, ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (2). The main goal of treatment for myocardial infarction (MI) is to reduce the size of infarct. The latest treatment modalities for MI with electrocardiographic evidence of STEMI consist of thrombolysis, percutaneous coronary intervention (PCI) and medical treatment (1, 3, 5). Reperfusion must be done early and prompt as time lost is equivalent to myocardium lost (1). Therefore, it is practicable to start thrombolysis therapy in the emergency department in order to reduce delay from first medical contact to cardiac reperfusion.

The use of streptokinase as thrombolytic agent is very common as it is effective and affordable. Mortality risk is significantly reduced by thrombolysis therapy with streptokinase, where it will restore the coronary patency (1). However, thrombolysis therapy is also associated with the increased risk of major bleeding events (4–7). In-hospital major bleeding is associated to short- and long-term mortality, stroke, MI, blood transfusion, as well as increased duration of hospital stay and cost (8). Clinical decisions should weigh between the risks of recurrent ischemia and major bleeding as both risks are associated with higher mortality rate (7).

The CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) score is one of the tools introduced to predict the risks of bleeding in NSTEMI patients (9, 10). This score was originally developed for NSTEMI patients, but was subsequently validated in STEMI patients (11). Previous studies reported that CRUSADE score was accurate in the prediction of major bleeding events (4). However, this score was created based on Caucasian population (5, 8), and limited studies have been performed to validate the application of CRUSADE score in the management of STEMI among the East Asian population. The score functions have not been evaluated in the Malaysian setting with different patient characteristics and treatment patterns, particularly in STEMI patients. Directly applying this prediction model may over or underestimate the bleeding risks. Therefore, this study was carried out to evaluate the association of the patient characteristics and clinical outcomes with major bleeding as well as to examine the prognostic value of CRUSADE risk score in predicting the in-hospital major bleeding among acute myocardial infarction (AMI) patients in Hospital Selayang.

Method

A single-centred retrospective study was carried out in Hospital Selayang, Selangor, Malaysia. This study was registered in the National Medical Research Register (NMRR) (ID No: NMRR-16-1817-32350) and ethics approval was granted by the Medical Research and Ethics Committee (MREC), Ministry of Health on 3rd July 2018.

All AMI patients aged above 18 years old who were admitted to Hospital Selayang and received a single dose of IV Streptokinase 1.5 million units from January 2015 to December 2018 were included in this study. Patients were excluded if they received double thrombolysis therapy (streptokinase and tenecteplase) or if they had taken oral anticoagulant prior to MI.

Sample size estimation was calculated using the population proportion formula (12). Prior data indicated that the proportion of major bleeding was 0.183 (13). If the Type I error probability and precision were 0.05 and 0.05, the targeted sample size was 167 patients.

Patients' demographic data and baseline laboratory data before streptokinase administration (i.e. hematocrit level, heart rate, systolic blood pressure, creatinine clearance-calculated using Cockcroft-Gault formula) were extracted from Hospital Selayang's electronic medical record and documented into the data collection form. All records throughout the hospital stay episode were checked and clinical outcomes such as major and minor bleeding, heart failure, cardiogenic shock and mortality were documented.

Patients were classified into two groups, namely major bleeding group and non-major bleeding group, based on the presence or absence of major bleeding. The definition of major and minor bleeding was shown in Table 1. Those with minor bleeding and no bleeding were grouped into the non-major bleeding group. CRUSADE risk score was calculated for every patient based on the baseline and clinical information collected. Table 2 showed the algorithm of CRUSADE risk score calculation (10), and Table 3 showed the risk stratification for CRUSADE risk scores.

Data were analysed using Statistical Package for Social Science (SPSS) version 21.0 and Microsoft Excel version 2013. Descriptive analysis such as frequency, percentage, median and interquartile range (IQR) were used to analyse the distribution of demographic data. Statistical tests such as Fisher's exact test (for categorical data) and Mann-Whitney test (for continuous data) were performed to compare the differences of demographics, baseline data and clinical outcomes between major bleeding and non-major bleeding groups. Meanwhile, to test the prognostic value of CRUSADE risk score, C-statistic or the area under the receiver operating characteristic (ROC) curve were used. C-statistics are commonly used in medical literature to evaluate a scoring system's capacity to distinguish between two groups of population that do and do not experience the outcome of interest. A C-statistic value of 0.5 and below suggests a very

poor model, while a value more than 0.7 suggests a good model (14). A p-value less than 0.05 was regarded as being statistically significant.

Table 1: Definition of Major and Minor Bleeding

Major Bleeding	Minor Bleeding
• Fatal bleed • ICB – confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) • Upper gastrointestinal bleed (UGIB) – confirmed by Oesophagus Duodenoscopy (OGDS) procedure • Retroperitoneal bleed • ≥ 5cm hematoma • Overt bleeding (including on imaging) with decrease Hemoglobin ≥ 5g/dl or Hematocrit ≥ 15% from baseline • Bleeding that causes substantial hemodynamic compromise that requires intervention or treatment (i.e. blood product transfusion/ Vitamin K/ Tranexamic acid).	• Gum bleeding • Spontaneous gross hematuria* • Spontaneous hematemesis* • Other bleeding not requiring treatment or causing hemodynamic compromise, resulting Hemoglobin drop by 3 – 5 g/dl or Hematocrit drop by 10 -15% (*even if hemoglobin or hematocrit drop was < 3g/dl or <10%, respectively)

Definition is based on the Thrombolysis in Myocardial Infarction (TIMI), Global Use of Strategies to Open Occluded Arteries (GUSTO) and ACUITY criteria of major/ severe bleeding(18, 20, 21)

Table 2: Algorithm to determine the CRUSADE risk score of in-hospital major bleeding

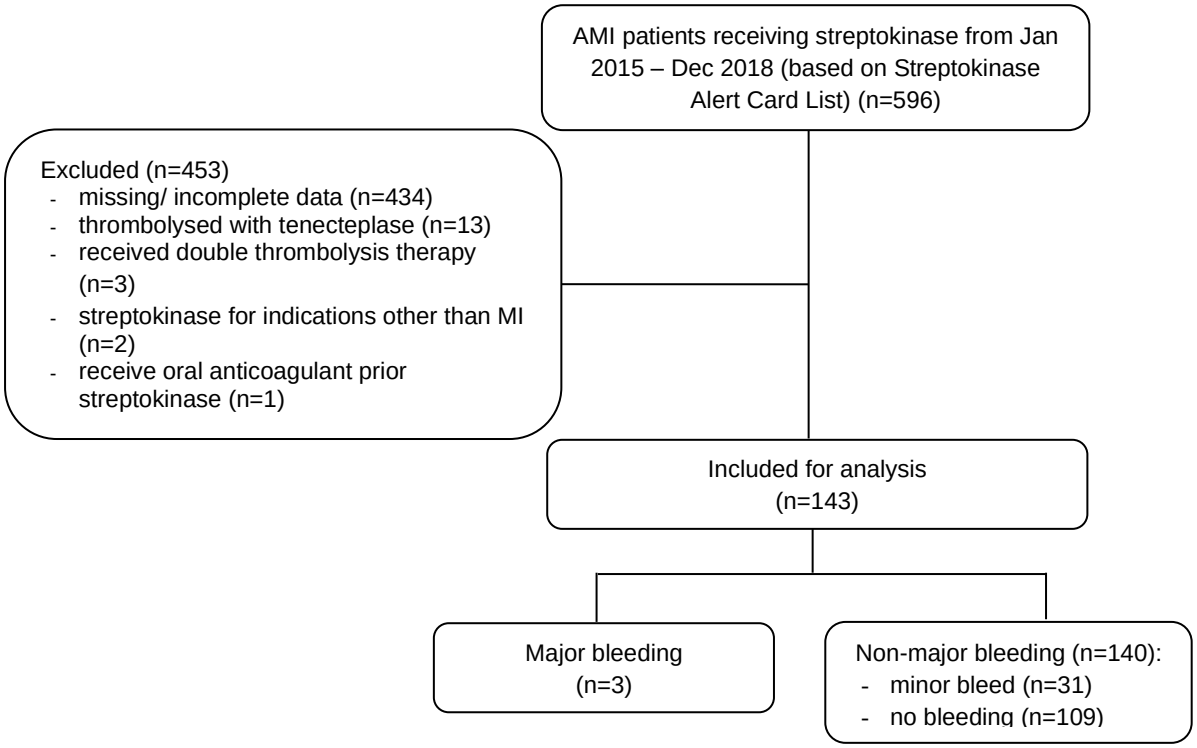
Predictor	Range	Score
Baseline Hematocrit	< 31	9
	31 – 33.9	7
	34 – 36.9	3
	37 – 39.9	2
	≥ 40	0
Creatinine Clearance	≤ 15	39
	> 15 – 30	35
	> 30 – 60	28
	> 60 – 90	17
	> 90 – 120	7
	> 120	0
Diabetes Mellitus	No	0
	Yes	6
Signs of Heart Failure	No	0
	Yes	7
Systolic Blood Pressure	≤ 90	10
	91 – 100	8
	101 – 120	5
	121 – 180	1
	181 – 200	3
	≥ 201	5
Heart Rate	≤ 70	0
	71 – 80	1
	81 – 90	3
	91 – 100	6
	101 – 110	8
	111 – 120	10
	≥ 121	11
Prior Vascular Disease	No	0
	Yes	6
Female Sex	No	0
	Yes	8

Table 3: CRUSADE Risk Score Stratification

Risk stratification	Score
Very Low	<20
Low	21 - 30
Moderate	31 - 40
High	41 - 50
Very High	>50

Results

The number of AMI patients receiving IV Streptokinase in Hospital Selayang from January 2015 to December 2017 were 596. A total of 143 patients met the inclusion criteria of this study (Figure 1). Only three patients (2.1%) were in the major bleeding group, while the remaining 140 (97.9%) were in the non-major bleeding group. There was no statistically significant difference in the demographics and baseline characteristics between the two groups (Table 4). There was also no significant difference in the CRUSADE risk score between the major bleeding and non-major bleeding group, with a median score of 23 (min, max 23, 33) and 25 (IQR 15), respectively.



Abbreviation: AMI = Acute myocardial infarction

Figure 1: Selection process of eligible patients

Table 4: Patient characteristics (n=143)

	Major Bleeding (n=3)	Non-Major Bleeding (n=140)	p- value
Age, median years (min, max / IQR)	54 (54, 73)	54 (14)	0.402[a]
Gender, n (%)			1.000[b]
Male	3 (100)	127 (90.7)	
Female	0 (0)	13 (9.3)	
Race, n (%)			0.561[b]
Malay	2 (66.7)	54 (38.6)	
Others	1 (33.3)	86 (61.4)	
Weight, median kg (min, max / IQR)	70 (60, 70)	70 (15)	0.656[a]
Smoker, n (%)	2 (66.7)	89 (64%)	1.000[b]
Co-morbidity, n (%)			
Diabetes	0 (0)	65 (46.4)	0.251[b]
Hypertension	2 (66.7)	68 (48.6)	0.614[b]
Dyslipidemia	0 (0)	26 (18.6)	1.000[b]
Prior vascular disease	0 (0)	5 (3.6)	1.000[b]
Ischemic heart disease	0 (0)	26 (18.6)	1.000[b]
Chronic kidney disease	0 (0)	10 (7.2)	1.000[b]
Heart Failure on admission, n (%)	0 (0)	32 (22.9)	1.000[b]
Baseline heart rate, median (min, max / IQR)	76 (52, 76)	86 (25)	0.132[a]
Baseline Systolic BP, median (min, max / IQR)	202 (109, 202)	138 (30)	0.260[a]
Baseline hematocrit, median (min, max / IQR)	48 (42, 48)	44 (6.8)	0.413[a]
Baseline CrCl, median ml/min (min, max / IQR)	61.7 (47.1, 61.7)	82.3 (38.9)	0.069[a]
Ejection fraction, median (min, max / IQR)	30 (30, 50)	40 (13)	0.516[a]
CRUSADE score, median (min, max / IQR)	23 (23, 33)	25 (15)	0.816[a]
Killip Class, n (%)			NA
Killip 1	2 (66.7)	85 (60.7)	
Killip 2	0 (0)	32 (22.9)	
Killip 3	0 (0)	5 (3.6)	
Killip 4	1 (33.3)	18 (12.9)	
Anticoagulant use in ward, n (%)			NA
Enoxaparin	0 (0)	15 (10.7)	
Fondaparinux	1 (33.3)	124 (88.6)	
Not on any	2 (66.7)	1 (0.7)	

[a] Mann-Whitney test, [b] Fischer exact test
Abbreviation: BP = Blood pressure; CrCl = Creatinine clearance (calculated using Cockcroft-Gault formula); IQR = Interquartile range

There were only three cases (2.1%) of major bleeding events observed in this study, while 31 patients (21.7%) had minor bleeding. Most of the bleeding cases occurred within 24-hour post streptokinase administration (20.3%), including all three cases of major bleeding. The types of bleeding identified were summarised in Table 5.

Table 5: Bleeding events observed in this study

Variables	Finding (n=143)
No bleeding, n (%)	109 (76.2)
Major Bleeding, n (%)	3 (2.1)
Intracranial bleeding	2 (1.4)
Hematoma	1 (0.7)
Minor Bleeding, n (%)	31 (21.7)
Gum bleeding	15 (10.5)
Spontaneous hematuria	6 (4.2)
Spontaneous hematemesis	3 (2.1)
Others	7 (4.9)
Bleeding onset, n (%)	
Within 24 hours	29 (20.3)
>24hours	5 (3.5)

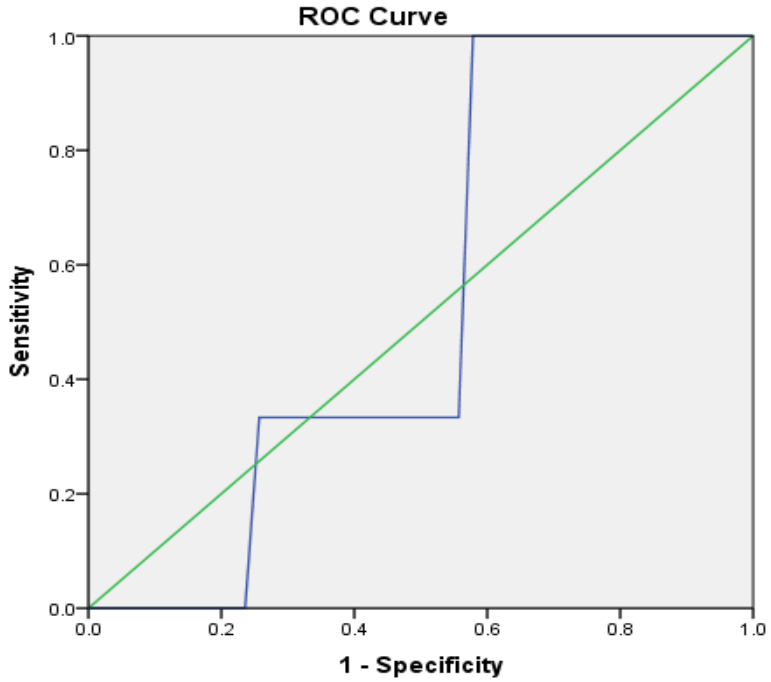
The clinical outcomes that were observed in this study were presented in Table 6. Mortality was found to be associated with major bleeding events in AMI patients receiving Streptokinase (p=0.013). Out of three patients with major bleeding, two patients (66.7%) were dead. Patients in the major bleeding group had a significantly longer duration of hospital stay as compared to non-major bleeding group (p=0.003). The median of hospital stay for major bleed group was 16 days, while non-major bleed group was only 5 days.

Table 6: Association of Clinical Outcomes During Hospital Stay with Major Bleed

	Major Bleeding (n=3)	Non-Major Bleeding (n=140)	p-value
Death, n (%)	2 (66.7)	8 (5.7)	0.013[b]
In-hospital heart failure, n (%)	0 (0)	3 (2.1)	1.000[b]
Cardiogenic shock, n (%)	1 (33.3)	17 (12.1)	0.334[b]
Length of hospital stay, median (min, max / IQR)	16 (10, 16)	5 (1)	0.003[a]

[a] Mann-Whitney test, [b] Fischer exact test
Abbreviation: IQR = Interquartile range

According to ROC curve in Figure 2, we were not able to determine a significant prognostic value of CRUSADE risk score in predicting major bleeding among AMI patients who receive Streptokinase (area under the ROC curve = 0.539; 95% CI 0.353-0.726; p = 0.816).



C=0.539; 95% CI 0.353-0.726; p=0.816
Abbreviation: ROC = Receiver operating characteristics; CI = Confidence interval

Figure 2: ROC curve for CRUSADE score with major bleeding events

Discussion

In this study, 2.1% of included patients experienced major bleeding. According to Al-Daydamony and Farag (4), the frequency of major bleeding ranged from 2% to 9% across the spectrum of acute coronary syndrome (ACS), based on the type of treatment employed, antithrombotic dosage and the invasive procedures commenced. Another study among the Netherlands population reported an incidence rate of 1% for intracranial bleeding (ICB) associated with thrombolytic therapy (15). Meanwhile, in the ISIS-2 study and ISG study, the incidences of major bleeding post Streptokinase were 0.5% and 0.9%, respectively (16).

We found that most of the bleeding events occurred within 24 hours (20.3%) after Streptokinase administration. This was comparable with a study done by McLeod et al. (17), where 15.9% of patients experienced bleeding events within 24-hour period after initiation of Streptokinase. This included those with

ICB. The first manifestation of acute bleeding observed after thrombolytic treatment was found to be ranging from three to 36 hours, with a median of 16 hours (15).

Even though there was no significant difference in the CRUSADE risk scores between patients with and without major bleeding, we found the association between major bleeding with in-hospital mortality. According to Fitchett (18), the incidence of ICB-associated thrombolysis was 0.64% to 0.94%, with an associated in-hospital mortality of almost 60% and the one-year mortality increased by five-folds. Those with major bleeding also have five times higher rates of 30-day mortality than those without major bleeding. In the GRACE registry, STEMI patients who developed major bleeding had the highest mortality rate as opposed to non-STEMI patients (22.8% vs 7%) (19).

Our study also demonstrated significantly longer hospital stay in major bleed group than those in non-major bleed group (p=0.003). Since major bleeding extended the hospital stay and increased resources consumption, it signified a source of excess expenditures (20). Minimising bleeding complications is therefore an important objective in MI management, which may favorably impact the morbidity and overall healthcare costs (18, 20).

Although several published studies demonstrated successful use of CRUSADE bleeding risk score in predicting major bleeding in various populations with ACS, our results showed the contrary. Al-Daydamony and his colleagues had studied the prognostic value of CRUSADE risk score in 240 patients with ACS, who were admitted to tertiary hospital in Egypt (4). They found that the validity of the CRUSADE risk model in predicting major bleeding was satisfactory across the ACS spectrum. The CRUSADE score ≥ 38.5 in prediction of major bleeding among STEMI patients treated with Streptokinase had the sensitivity of 70% and specificity of 85% (C=0.79) (4). CRUSADE risk score has also been evaluated in the Southeast Asia population. Jinatongthai had studied the use of CRUSADE risk score in Thai patients with ACS receiving enoxaparin (13). Their findings showed a satisfactory discriminatory capacity for the entire study population (C=0.688), unstable angina (C=0.591), NSTEMI (C=0.693) and STEMI (C=0.736). They concluded that CRUSADE score was able to predict major bleeding among Thai patients with ACS treated with enoxaparin.

On the other hand, there were also studies that reported that CRUSADE risk score had a poor predictive ability for major bleeding in certain subgroups. In a study among 544 non-ST elevation-acute coronary syndrome (NSTE-ACS) patients with age more than 80 year-old, Faustino et al. found that CRUSADE risk score had a weak discriminatory capacity for major bleeding (C=0.51) (21). Similar finding was reported by Ariza-Sole et al. where CRUSADE risk score had a lower predictive performance among ACS patients aged more than 75 year-old (C=0.63) as compared to those younger than 75 year-old (C=0.81) (22). CRUSADE risk score performance was also modest in patients who were previously on oral anticoagulants (C=0.615) and in those who did not undergo cardiac catheterization (C=0.628) (23). The discriminating power of the CRUSADE risk score in ACS patients varies significantly. This could be related to a variety of factors that make assessment of bleeding risk difficult, such as age, co-morbidities, treatment with antithrombotic agents, conservative or invasive management, and site of vascular access for angiography (24).

Since this was a retrospective study, the findings may not be sufficient to influence the current practice. However, the results obtained can be used to provide preliminary information regarding the characteristics of patients who received streptokinase and its association with major bleeding. Another limitation is that this study was conducted in a single center, hence, the results produced could not be generalised to all Malaysian populations with STEMI. The small sample size in the major bleeding group may had reduced the statistical power of this study. Also, the huge difference in sample size between the major bleeding and non-major bleeding groups could had severely impacted the data analysis, which might underestimate the true value of CRUSADE risk score.

Conclusion

This was the first study to evaluate the CRUSADE risk score in predicting major bleeding events post Streptokinase administration among AMI patients in Malaysia. We did not find any significant association between patient demographics and baseline clinical characteristics with major bleeding post streptokinase administration in AMI patients. Nonetheless, our results showed that major bleeding was associated with in-hospital mortality and length of hospital stay. This study could not demonstrate the prognostic value of

CRUSADE risk score in predicting major bleeding in AMI patients treated with streptokinase. Studies with a larger population is needed in the future to verify our findings.

Acknowledgement
First of all, we thank the Director General of Health Malaysia for his permission to publish this article. We would like to extend our gratitude to Dr Richard Bach from Washington University School of Medicine, as one of the founders of CRUSADE risk score, for giving us permission to use the score in our study. Our warmest thanks and appreciation also go to everyone who has involved either directly or indirectly in the completion of this study.

Conflict of interest statement
The authors declare that there is no conflict of interest.

References
1. Chaudhary A, Bhusare DB, Ahmed K, Vyawahare R, Biyani A. Analysis of Streptokinase as Fibrinolytic Agent in Patients with STE Elevation Myocardial Infarction. Global Journal for Research Analysis [Internet]. 2017 [cited 2018 Mac 17];6(7):1-3. Available from: https://www.worldwidejournals.com/global-journal-for-research-analysis-GJRA/fileview/July_2017_1500119267__01.pdf
2. World Health Organization [Internet]. Geneva; 2020. Health Estimates 2020: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2019 [cited 2023 Dec 6]. Available from: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death
3. Kietzmann T. Myocardial infarction in elderly patients: How to assess their bleeding risk? Thromb. Haemost [Internet]. 2015 [cited 2018 Apr 12]; 114: 869-871. DOI: 10.1160/TH15-06-0507.v
4. Al-Daydamony MM & Farag EM. CRUSADE bleeding score as a predictor of bleeding events in patients with acute coronary syndrome in Zagazig University Hospital. Indian Heart J [Internet]. 2016 [cited 2018 Feb 7]; 68(5): 632-638. DOI: 10.1016/j.ihj.2016.03.007.
5. Liu R, Zheng W, Zhao G, Wang X, Zhao X, Zhou S, et al. Predictive Validity of CRUSADE, ACTION and ACUITY-HORIZONS Bleeding Risk Scores in Chinese Patients With ST-Segment Elevation Myocardial Infarction. Circ. J [Internet]. 2018 Feb 23 [cited 2018 Mac 17]; 82: 791-797. Available from: https://doi.org/10.1253/circj.CJ-17-0760
6. Bundhun PK, Janoo G, Meng-Hua C. Bleeding events associated with fibrinolytic therapy and primary percutaneous coronary intervention in patients with STEMI. Medicine [Internet]. 2016 [cited 2018 Mac 17]; 95(23): 1-9. DOI: 10.1097/MD.0000000000003877
7. Correia LCL, Ferreira F, Kalil F, Silva A, Pereira L, Carvalhal M, et al. Comparison of ACUITY and CRUSADE Scores in Predicting Major Bleeding during Acute Coronary Syndrome. Arq Bras Cardiol [Internet]. 2015 [cited 2018 Mac 17]; 105(1): 20-27. DOI: 10.5935/abc.20150058
8. Liu R, Lyu S, Zhao G, Zheng W, Wang X, Zhao X, et al. Comparison of the performance of the CRUSADE , ACUITY-HORIZONS , and ACTION bleeding scores in ACS patients undergoing PCI: insights from a cohort of 4939 patients in China. J. Geriatr. Cardiol [Internet]. 2017 Feb [cited 2018 Mac 17]; 14: 93-99. DOI: 10.11909/j.issn.1671-5411.2017.02.011
9. Bang J, Young S, Hyun M, Serebruany V. CRUSADE Score is Superior to Platelet Function Testing for Prediction of Bleeding in Patients Following Coronary Interventions. EBioMedicine [Internet]. 2017 [cited 2018 Mac 17]; 21: 213-217. Available from: https://doi.org/10.1016/j.ebiom.2017.05.010
10. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, 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 [Internet]. 2009 [cited 2018 Mac 13]; 119: 1873-1882. DOI: 10.1161/CIRCULATIONAHA.108.828541
11. Sánchez-martínez M, Flores-blanco PJ, Lopez-Cuenca AA, Sanchez-Galian MJ, Guerrero-Perez E, Ma. Valdes, et al. Evaluation of the CRUSADE Risk Score for Predicting Major Bleeding in Patients with Concomitant Kidney Dysfunction and Acute Coronary Syndromes. Cardio Ren. Med [Internet]. 2017 [cited 2018 Mac 12]; 7: 179-187. DOI: 10.1159/000455102
12. Lemeshow S, Hosmer WD, Klar J, Lwanga KS. Adequacy of sample size in health studies [Internet].

Chichester (England): J. Wiley for the World Health Organization; 1990 [cited 2018 Jun 1]. Available from: http://apps.who.int//iris/handle/10665/41607.
13. Jinatongthai P, Khaisombut N, Likittanasombat K, Chaiyakunapruk N, Watcharathanakij S, Nathisuwan S. Use of the CRUSADE bleeding risk score in the prediction of major bleeding for patients with acute coronary syndrome receiving enoxaparin in Thailand. Heart, Lung and Circulation [Internet]. 2014 [cited 2018 Mac 17]; 23(11): 1051-1058. Available from: https://doi.org/10.1016/j.hlc.2014.05.002
14. Stephanie Glen. C-statistic: Definition, Examples, Weighting and Significance [Internet]. Statistics How To. [cited 2023 Dec 6]. Available from: https://www.statisticshowto.com/c-statistic/
15. Jaegere PPDE, Arnold AA, Balk AH, Simoons ML. Intracranial Hemorrhage in Association With Thrombolytic Therapy: Incidence and Clinical Predictive Factors. J. Am. Coll. Cardiol [Internet]. 1992 [cited 2018 Mac 17]; 19(2): 289-294. DOI: 10.1016/0735-1097(92)90480-b
16. Kafetz K, Luder R. Safe use of streptokinase in myocardial infarction in patients aged 75 and over. Postgr. Med J [Internet]. 1992 [cited 2018 Mac 20]; 68: 746-749. DOI: 10.1136/pgmj.68.803.746
17. McLeod D, Thayer C, Perfetto E, Hartzema A. Pharmacoepidemiology of bleeding events after use of r-alteplase or streptokinase in acute myocardial infarction. Ann. Pharmacother [Internet]. 1993 [cited 2018 Mac 13]; 27(7-8): 956-962. DOI: 10.1177/106002809302700725.
18. Fitchett D. The impact of bleeding in patients with acute coronary syndromes: How to optimize the benefits of treatment and minimize the risk. Can. J. Cardiol [Internet]. 2007 [cited 2018 Mac 17]; 23(8): 663-671. DOI: 10.1016/s0828-282x(07)70229-5
19. Khanolkar UB, Annamalai R. CSI: Cardiology Update 2016 [Internet]. India: Jaypee Brothers Medical Publishers; 2017. Chapter 16, How to Manage Bleeding following Thrombolysis? [cited 2018 Feb 26]. DOI: 10.5005/jp/books/13035_17.
20. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas CMsGD, Kirtane AJ, et al. A Risk Score to Predict Bleeding in Patients With Acute Coronary Syndromes. J. Am. Coll. Cardiol [Internet]. 2010 [cited 2018 Mac 14]; 55(23): 2556-2566. DOI: 10.1016/j.jacc.2009.09.076
21. Faustino A, Mota P, Silva J. Non-ST-elevation acute coronary syndromes in octogenarians: applicability of the GRACE and CRUSADE scores. Rev. Port. Cardiol [Internet]. 2014 [cited 2023 Oct 04]; 33(10): 617-627. Available from: http://dx.doi.org/10.1016/j.repc.2014.01.025
22. Ariza-Solé A., Formiga F, Lorente V, Sanchez-Salado JC, Sanchez-Elvira G, Roura G, et al. Efficacy of bleeding risk scores in elderly patients with acute coronary syndromes. Rev. Esp. Cardiol [Internet]. 2014 [cited 2023 Oct 04]; 67: 463-470. Available from: http://dx.doi.org/10.1016/j.rec.2013.10.008
23. Abu-Assi E, Raposeiras-Roubin S, Lear P, Cabanas-Grandío P, Girondo M, Rodríguez-Cordero M, et al. Comparing the predictive validity of three contemporary bleeding risk scores in acute coronary syndrome. Eur. Heart. J. Acute Cardiovasc Care [Internet]. 2012 [cited 2023 Oct 04]; Sep;1(3):222-31. DOI: 10.1177/2048872612453924.
24. Bento D, Marques N, Azevedo P, Guedes J, Bispo J, Silva D, et al. CRUSADE: Is it still a good score to predict bleeding in acute coronary syndrome? Rev. Port. Cardiol [Internet]. 2018 [cited 2023 Oct 04]; 37: 889-897. Available from: https://doi.org/10.1016/j.repce.2018.02.020.