ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

CRUSADE Bleeding Score as a Predictor for the Risk of Bleeding Events in Patients with Acute Coronary Syndrome: A Prospective Study from Tamil Nadu

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Abstract

Background: The CRUSADE bleeding risk score is an accurate and robust risk-stratification tool for predicting hemorrhagic complications in patients with Acute Coronary Syndrome (ACS). However, studies assessing and validating this score especially within Indian population are scarce to almost non-existent. Objective: To evaluate the Crusade Bleeding Score in predicting the risk of bleeding events in patients with acute coronary syndrome. Methods: This cross-sectional study was conducted at a secondary care hospital in Tamil Nadu, India. A total of 72 patients with ACS on treatment with anti-thrombotics that fulfilled the inclusion criteria of the study were prospectively recruited. The patient's demographic data along with their past medical history pertinent to the study was collected and the scores for each patient were calculated. Results: Significant major bleeding was found among considerably older, female patients, diabetic and hypertensive patients, as also among patients having lower GFR values. Five patients classified under the Very High-Risk Category of the CRUSADE bleeding score further went on to develop hemorrhagic complications thereby validating the score among the study population. Conclusion: The CRUSADE bleeding score was found to be an accurate predictor of bleeding events within our study population with good validity. We further recommend the suitable use of the CRUSADE bleeding risk score in clinical practice as there is a need for stronger evidence to support the use of risk stratification systems to optimize therapy and improve patient outcomes in India.

Keywords: *Acute coronary syndrome, Anticoagulants, Anti platelets, Bleeding Risk, Crusade Bleeding Score.*

Introduction

Coronary artery disease (CAD) is one of the prime causes of death in India from the past two decades [1].Antithrombotic therapy being its mainstay of treatment, hemorrhagic complications are very common [2]. Hemorrhagic manifestations of antithrombotic therapy contribute to substantial morbidity, mortality with an incidence of 6.7% major bleeding and 0.32 % fatalities, health related costs and costs to society [3, 4].

Hence, it's necessary to foresee the risk of bleeding events in patients with acute coronary syndrome (ACS) to improve their treatment outcomes. There are various scoring systems such as grace, ACUITY-horizons, actions etc. employed to predict the bleeding risk among patients with ACS on anti-thrombotics [5, 6].

Among these, Can Rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines (CRUSADE) has gained noticeable interest due to its high sensitivity and specificity [7-13]. So far, CRUSADE bleeding risk score has not been validated within the Indian population. This study aims at predicting the risk of bleeding in patients with Acute Coronary Syndrome on anti-thrombotics and to validate CRUSADE score for the south Indian population.

Materials and Methods

Study Design and Setting

The study was carried out at Intensive Care Unit, General medicine departments of Government District Headquarters Hospital which is a 450 bedded secondary care hospital in Ooty, Nilgiris District of Tamil Nadu, India. This study design was prospective, cross sectional in nature and carried out from August 2018 to March 2019. The approval was sought from the Institutional Ethics Committee of the hospital. A convenient sampling method was opted for ease of data collection. Informed consent was obtained and patient selection criteria followed is illustrated in Figure 1 [9].

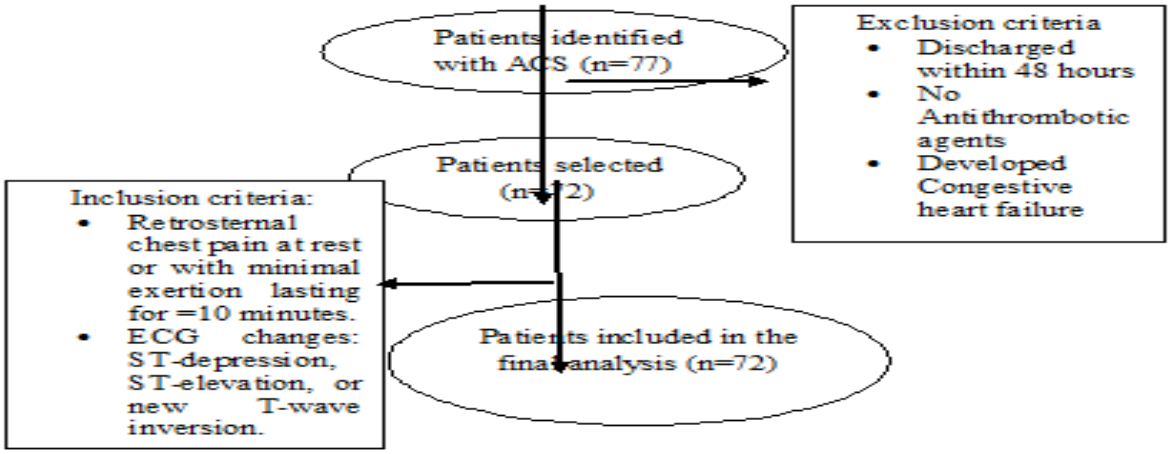


Fig. 1: Patient selection criteria

Patient demographics and outcome data obtained from the hospital were logged into the data collection form. The data along with the calculated CRUSADE bleeding score for individual patient was then entered into spreadsheet (Excel, Microsoft office).

Statistical analysis

A descriptive analysis was performed for patient demographics and presented as proportions or mean ± standard deviation (SD) as appropriate. The 95% confidence intervals and *p*-values were calculated as per the normal approximation of the binomial distribution. The differences between continuous variables were estimated using unpaired Student's t-test and one-way ANOVA. The independent student t-test was done using Graph Pad Prism version 7.00 for Windows (Graph Pad Software, La Jolla California USA, www.graphpad.com.).

All *p*-values were expressed as the results of two-tailed tests and *p*-values <0.05 were considered statistically significant. The Regression Output in MS Excel was also employed to determine the coefficient of determination between two variables among assessed patient parameters.

Results

Patients were allocated bleeding scores based on the values of their parameters entered in the CRUSADE scoring system as described in Table 1.

Table 1: Patient parameters assessed in the CRUSADE Scoring System

Parameter	Range	Score	Parameter	Normal value	Score
Baseline Hematocrit (%)	<31	9	Systolic Blood Pressure on admission (mmHg)	91-100	8
	31-33.9	7		101-120	5
	34-36.9	3		121-180	1
	37-39.9	2		181-200	3
				≥201	5
Baseline Creatinine Clearance (mL/min)			Heart Rate on Admission (beats/min)		
	>15-30	35		71-80	1
	>30-60	28		81-90	3
	>60-90	17		91-100	6
	>90-120	7		101-110	8
	>120	0		111-120	10
Diabetes Mellitus			Prior Vascular Disease	≥121	11
	Yes	0		No	0
	No	6		Yes	6
Signs of Heart Failure	Yes	0	Female Sex	No	0
	No	7		Yes	8

Using the CRUSADE bleeding score thus obtained, the study subjects were classified into five groups as presented in Table 2.

Table 2: Risk stratification of patients based on CRUSADE Score

Stratification of Bleeding Risk	Very low Risk ≤20	Low Risk 21 to 30	Moderate Risk 31 to 40	High Risk 41 to 50	Very High Risk >50	Average
Average Bleeding Score	15.5	26.83	35.47	44.28	58.82	
Average Age (In Years)	51.87	57.33	57.52	58.71	64.11	58.7±11.6
Number of Females	0	1	2	7	13	
Number of Males	8	11	19	7	4	
Average Serum Creatinine (mg/dL)	0.81	0.95	1.21	1.06	1.9	1.2±0.5
Average Hematocrit (%)	43.82	42.9	47.49	38.99	39.31	42.7±7.9
Glomerular Filtration Rate (mL/min)	121.87	104.72	77.52	77.64	41.76	78.6±29.6
Prior Vascular Disease: Yes	1	8	15	12	13	
Prior Vascular Disease: No	7	4	6	2	4	
Diabetes Mellitus: Yes	0	1	1	6	8	
Diabetes Mellitus: No	8	11	20	7	9	

As shown in Table 3, female patients showed higher CRUSADE bleeding scores when compared to male patients in the study (95% CI, 13.68-25.17; two tailed p value 0.0001) where [t=6.7478, df =70 and standard error of difference =2.879]. Similarly, patients with prior vascular disease denoted a statistically significant difference with higher CRUSADE bleeding scores in contrast to patients without any prior vascular disease within our study (95% CI, 3.88-17.71; two tailed p value = 0.0027) where [t=3.1145, df =70 and standard error of difference =3.466]. Diabetic patients revealed higher CRUSADE bleeding scores compared to Non-Diabetic patients (95% CI, 3.88-17.71; two tailed p value= 0.0027) where [t=3.1145, df =70 and standard error of difference=3.466]. However, no significant difference was observed between patients <65 years of age when compared to patients>65years of age within our study (95% CI,-670.37-74.84; two tailed p value = 0.0027) where [t=1.5941, df =69 and standard error of difference =186.782].

Table 3: Comparison of CRUSADE bleeding scores within different risk factors

Category			***p value**
Gender	Male	Female	
	32.84±11.19	52.26 ±11.80	**0.0001
Prior Vascular Disease	Yes	No	
	42.49±13.90	31.70 ±13.29	**0.0027
Diabetes Mellitus	Yes	No	
	51.06±10.67	35.61±13.69	**0.0001
Age	<65 Years 36.82±14.13	>65 Years 44.43±14.40	*0.0426

(*p< 0.05, ** p<0.001Two-tailed p-value from unpaired student t-test)

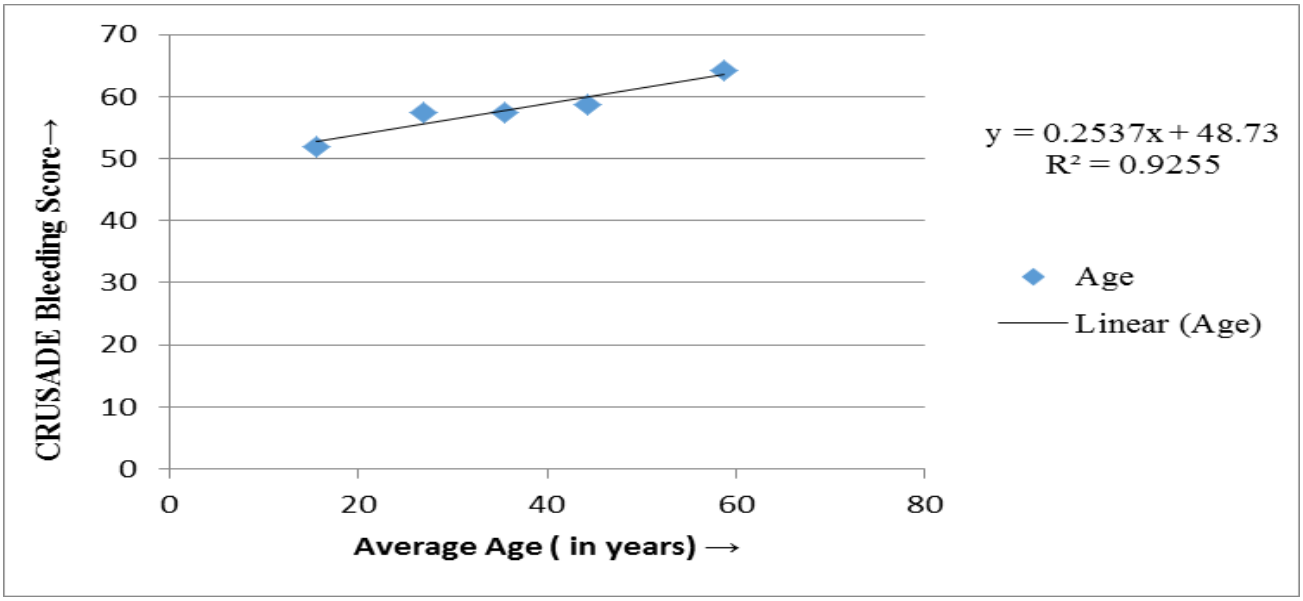
One-way ANOVA was employed to compare treatments among the 4 groups: patients treated with heparin, aspirin and clopidogrel (group 1, n= 39); those on aspirin and

clopidogrel, (group 2, n = 28), patients on clopidogrel alone (group 3, n=3); and aspirin alone (group 3, n= 2) respectively as depicted in Table 4. Within-group comparison showed significant differences between different treatment options (ANOVA, p =0.043229). However, a larger sample size with longer study duration is essential to analyze the key differences within the different treatment groups.

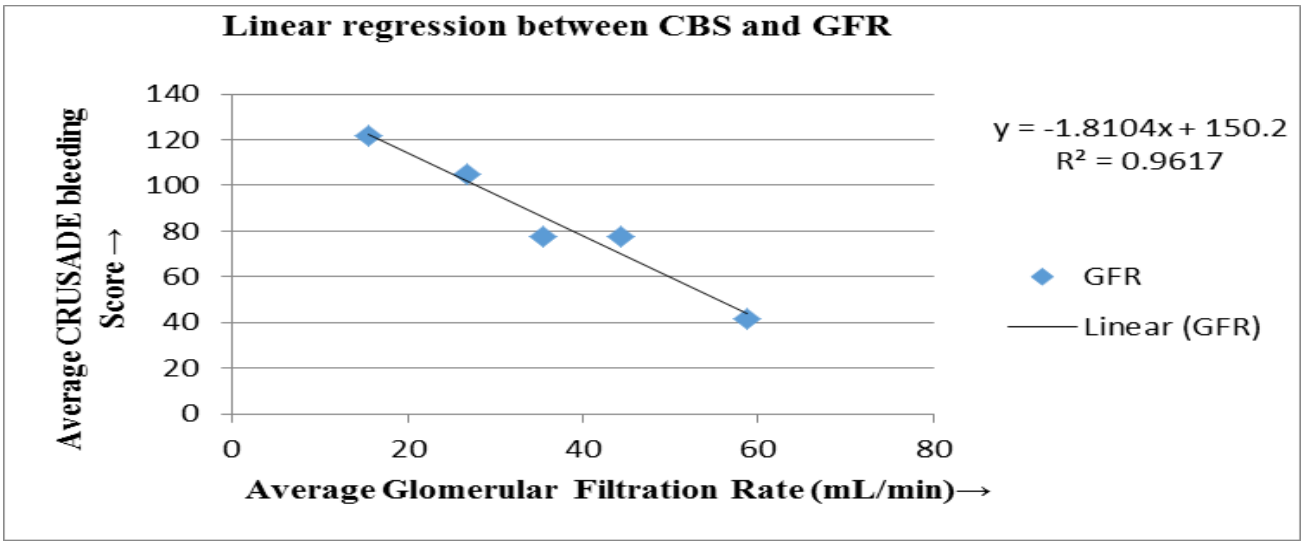
Table 4: Comparison within four treatment groups

	Sample				
	Patients on Heparin+ aspirin+ clopidogrel	Patients on aspirin+ clopidogrel	Patients on clopidogrel	Patients on aspirin	Total
N	39	28	3	2	72
Σ X	1638	962	145	100	2845
Mean	42	34.3571	48.3333	50	39.5139
Σ X^2	76566	36430	7187	5072	125255
Variance	204.4737	125.127	89.3333	72	180.8167
Standard deviation	14.2994	11.186	9.4516	8.4853	13.4468

A linear strong positive correlation (R^2 = 0.9255) [normal range 0-1] was obtained between the average CRUSADE bleeding score of patients within different risk categories and the average age of the study population as described in the Figure 2(A).



(A)



B

Fig 2: (A) Linear regression between average CRUSADE bleeding scores and Average age of the patients. (B) Linear regression between average CRUSADE bleeding scores and Average Glomerular filtration rate (GFR) of the patients

Contrary to this, a linear strong negative correlation (R^2 =0.9617) was obtained between the average CRUSADE bleeding score of patients within different risk categories and the average GFR values of the study population as described in the Figure 2(B). Subsequently, five patients developed adverse drug reactions (ADRs) of which three were cases of hematuria, one case of gum bleeding and one of hemorrhagic stools. Their clinical data is outlined in Table 5.

Table 5: Data of patients who developed adverse drug reactions

Name of the patient	CBS	Age	Serum creatinine (mg/dL)	Hematocrit (%)	GFR	PVD yes/no		DM yes/no
A	49	55	1.5	44	60	Yes		Yes
B	44	61	0.7	37.5	77	Yes		No
C	54	64	1.9	35.9	36	Yes		Yes
D	57	70	1.2	37.4	61	Yes		Yes
E	59	52	2.6	41.5	32	Yes		Yes
AVERAGE	52.6	60.4	1.58	39.26	53.2			

CBS- Crusade Bleeding Score

Discussion

Antithrombotic therapy employed in the management of ACS decreases the development of ischemic risk but relatively increases the bleeding risk [14]. Non-ST elevation acute coronary syndrome (NSTEACS) is treated with a combination of anti-platelets such as aspirin, clopidogrel and anticoagulants such as heparin and coumarin derivatives. Even though the tendency for bleeding complications have considerably reduced with newer drugs, still it poses as a major health burden to individuals.

Traditional way of assessing the risk of bleeding is by using Prothrombin Time International Normalized Ratio (PT INR). This method is inconvenient attributing to invasive procedures and also non-affordable cost for the poor patients. Due to limited lab facilities, many hospitals in India depend on empirical management of ACS leading to inappropriate dose adjustments and associated bleeding risk. In this context, use of a validated bleeding score such as CRUSADE serves as a convenient and cheap alternative.

Therefore, minimizing bleeding manifestations is imperative in the pharmacological management of ACS patients as it also decreases expenditure attributed to major bleeding and improve overall patient health related quality of life [15]. The risk for anticoagulant-related bleeding is predominantly highest at the commencement of treatment. The risk of major bleeding with anticoagulants largely depends on patient risk factors as such increase in age, female sex, decrease in GFR, co-morbidities diabetes mellitus or hypertension [16]. Female patients in our study showed significantly higher CRUSADE bleeding scores when compared to the male patients [17]. The exact cause or mechanism for the same remains unclear, untapped and requires further studies in this direction for better clarification. A statistically significant difference of higher CRUSADE bleeding scores in patients with prior vascular disease in contrast to patients without any prior vascular disease (p= 0.0027) was observed [18].

The study population comprised of ACS patients undergoing percutaneous coronary intervention. Patients with prior vascular disease may have a longer duration of exposure to antithrombotic agents increasing their risk for bleeding manifestations. Diabetic patients in our study revealed higher CRUSADE bleeding scores with statistically significant difference when compared to Non-Diabetic patients which is contradicting the data from other studies [19].

As Diabetes triggers the development of macrovascular (cardiovascular) complications, pre-existing abnormalities in small-vessels caused by metabolic stress shall be considered factorial for increased bleeding risk. Also, during anticoagulant therapy glucose control may be essential although it remains unclear if the level of glucose control can influence the risk of bleeding.

Similarly, a statistically significant difference was also observed between adults (Patients <65 years of age) when compared to geriatric

patients (≥65years of age) where the CRUSADE bleeding score was higher in patients above 65 years of age within our study [20, 21]. Decreasing GFR values in patients lead to an increase in CRUSADE bleeding scores; thus, patients with increasing severity of renal impairment will have higher bleeding scores [22].

Platelet dysfunction has been urged to be the chief factor responsible for hemorrhagic tendencies in advanced chronic kidney disease and is likely to be multifactorial. The bleeding complication commonly affects the gastrointestinal tract, soft tissues, and urinary tract manifesting as hematuria, gum bleeding, thrombocytopenia, melaena etc. The characteristics of patients who developed in-hospital adverse drug reactions comply with the risk prediction as given by their respective CRUSADE bleeding scores.

Patients with very high risk of bleeding scored more than 50 and the average CRUSADE bleeding score of these patients is 52.6. This proves that the CRUSADE bleeding score is reliable in predicting appropriate bleeding risk for patients as further patients with high and very high risk can be closely monitored to prevent the development of adverse drug reactions.

All these patients were found to have prior vascular disease and diabetes mellitus (except 1).Among these patients, the average age was observed to be 60.4 years, the average serum creatinine level was 1.58 mg/dL, the average hematocrit level was observed to be 39.26% and the average glomerular filtration rate was 53.2 mL/min as specified.

Thus, a small-scale validation within these five patients of the prediction accuracy of the CRUSADE bleeding score was also carried out in the process. The prescribing pattern of antiplatelet and oral anticoagulant agents among patients classified into different stages of renal failure based on their GFR values was observed.

Aspirin is safe to use in any stage of renal failure as opposed to other non-steroidal anti-inflammatory drugs that lower the renal blood flow [23].While unfractionated heparin is metabolized primarily within the liver and endothelium, thereby not requiring dose adjustment in stage four to five CKD which suggests it may be safely employed in any stage of renal disease [24].However, judicious use of Clopidogrel must be warranted in stage 5 of chronic kidney disease due to lack of clinical data in the specific sub-population.

Limitations of the Study

Our study had few limitations restricting the wider scope of the study. Clinical events after hospital discharge were not captured, precluding conclusions about optimal management strategies. Our observations were based on a small population with a short duration of study. Ours was a single centered study. A multi centre study would have created better impact on the results produced.

Conclusion

The CRUSADE bleeding risk score having been developed in an American hospital setting still displayed good validity within our study population and thus, we conclude that it is a reliable and accurate predictor of bleeding events. There is a need for stronger evidence to support the use of risk stratification systems. Thus, we further recommend the frequent use of the CRUSADE bleeding risk score in clinical settings and stress the need for studies in larger population for a longer duration within India.

Acknowledgement

The authors express their sincere thanks to Dr.KP Arun, Assistant Professor, Department of Pharmacy Practice for his intellectual support in completing this work.

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