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Original Article

Incidence and predictors of bleeding among Egyptian patients presenting with acute coronary syndrome: Using CRUSADE risk score

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ABSTRACT

Background: Early invasive strategies; in management of acute coronary syndrome; has led to improvement of patient outcomes. However, these invasive therapies have their own risks, namely bleeding and blood transfusion.

The aim of this study was to determine the incidence of bleeding, its location and severity among the study population, to correlate between the patients' characteristics and the risk profile of the patients based upon the CRUSADE risk score and increased bleeding events, and lastly; to identify the predictors of increased bleeding risk among Egyptian patients who presented with acute coronary syndrome.

Methods: The study had included eight hundred and twenty-three patients referred to coronary care unit (CCU), to (Ain Shams University hospital, Specialized Ain Shams hospital, and 6th October insurance hospital) with diagnosis of Acute Coronary Syndrome "ACS" within a period from 1/2014 till 7/2014, and they were followed up for additional three months following discharge with assessment of their bleeding risk and risk scores.

Results: More bleeding events had been witnessed among the study population who were older, diabetics, had renal impairment, had peripheral vascular disease, had congestive heart failure picture at presentation; more among female sex category and more among patients receiving GPIIbIIIa antagonists. Those bleeding events had been experienced during hospital stay.

Conclusion: Risk of bleeding can be evaluated using a simple risk score in both STEMI & NSTEMI patients, and across anti-coagulant strategies, providing important prognostic information. Variability in the rates of bleeding is likely based on differences in baseline characteristics, comorbidities, and invasive treatment strategies rather than specific anti-coagulation regimens. Patients at highest risk of bleeding are also at highest risk of ischaemia and thrombotic complications. Thus higher risk patients need a more careful treatment approach to maximize the efficacy of therapy and to reduce thrombotic risk while reducing the bleeding risk.

1. Introduction

There has been great development in management of acute coronary syndromes (ACS). This has led to improvement of patient outcomes. Early invasive strategies in high-risk patients are proving better results. However, these invasive therapies have their own risks, namely bleeding and blood transfusion.[1,2]

Bleeding is associated with increased risk of both short- and long-term events (including MI, stroke and death) among patients with ACS. Also, the safety of blood transfusion has been called into question, suggesting that the appropriate management strategy maintaining adequate anticoagulant effect to decrease ischaemia, and minimizing the risk of bleeding, may improve ACS outcomes.[3,4]

Rates of major bleeding in ACS have ranged from 0.8% to 11.5%, and according to studies; it is the most common non-cardiac complications of anti-ischemic therapy in those patients.[5–7]

The CRUSADE bleeding risk score had addressed 8 baseline characteristics associated with risk of major bleeding: heart rate, systolic blood pressure, baseline hematocrit value, creatinine clearance, female gender category, diabetes mellitus, congestive heart failure, and prior vascular disease.[8]

There are many bleeding schemes namely TIMI, REPLACE-2 and GUSTO. GUSTO classification is based on clinical events and categorizes bleeding as severe life threatening, moderate, and mild. TIMI

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classification is based on laboratory values and categorizes bleeding as major, moderate, or minor. The GRACE registry defined major bleeding as life threatening event requiring transfusion of two or more units of packed red blood cells, or resulting in absolute decrease in the hematocrit value of 10% or more or death, or haemorrhagic subdural haematoma.[9,10]

2. Subjects and methods

The study had included eight hundred and twenty-three of patients referred to coronary care unit (CCU), to Ain Shams University hospital, Specialized Ain Shams hospital, and 6th October insurance hospitals with diagnosis of Acute Coronary Syndrome "ACS" within the period from 1/2014 till 7/2014. All patients were followed up for additional three months following discharge.

Relevant exclusion criteria included patients with

1. Stable coronary artery disease.
2. Advanced renal disease.
3. Advanced hepatic disease.
4. Contraindications to cardiac catheterization (severe infections, severe anemia, debilitating diseases, malignancy and blood dyscrasias).

Patients were monitored for clinical outcomes and adverse events during their hospitalization, and for first three months after discharge.

The patients were subjected to

1. C***omplete medical*** history *taking* with special emphasis on:
   A. History of previous bleeding tendency and the medications they received.
   B. History of risk factors for coronary artery disease including: age, gender, Hypertension, diabetes mellitus, smoking status, renal impairment, stroke and peripheral vascular disease .
   C. Symptoms of congestive heart failure, demonstrated by exertional dyspnea, orthopnea, and fatigue either at rest or exertional.
2. ***Physical examination*** was performed with special emphasis on:
   A. Local cardiac examination for signs of congestive heart failure including rales >1/3 lung fields, elevated JVP, S3 gallop and/or signs of cardiogenic shock.
   B. Examination of access -site searching for hematomas and ecchymotic patches.
   C. Examination of peripheral pulsations to rule out absent peripheral pulsations both before coronary angiogram raising possibility of peripheral vascular disease as well as post coronary angiogram searching for possible vascular complications.
3. ***Laboratory investigation:***
   – Blood samples for complete blood count and creatinine measurements were collected on hospital admission before institution of therapy.
   – Creatinine clearance was calculated from baseline creatinine values using the Cockcroft and Gault equation with adjustment for sex, also blood samples were taken at the time of admission for CBC (Hb% & Hct), S. Creatinine, INR, Cardiac enzymes: (CK, CKmb, TnI).
4. ***ECG*** was performed within 10 min of presentation to determine eligibility of emergent reperfusion strategy in STEMI or early invasive strategy versus conservative in NST-ACS .
5. *Therapies, interventional procedures and frequency of major bleeding.*
   - Pre-hospital:
     – Aspirin.
     – Clopidogrel.
   - Hospital therapies:

   A. Antiplatelet:
   Aspirin, Clopidogrel, Glycoprotein IIb/IIIA receptor blockers.
   B. Anti-coagulants:
   Unfractionated heparin, Low molecular weight heparin, warfarin
   C. Thrombolytics if any.
   D. Interventional procedures:
     – Percutaneous coronary intervention.
     – CABG.
6. *Assessment of bleeding and bleeding risk scores:*

A. **GUSTO-bleeding score:** had defined bleeding as either:
   1. Intracranial hemorrhage or a >5 g/dl decrease in the hemoglobin concentration or a hemorrhage or bleeding that causes hemodynamic compromise and requires intervention (severe *or life threatening*).
   2. Bleeding that requires blood transfusion but does not result in hemodynamic compromise (*moderate*).
   3. Bleeding that does not meet criteria for either severe or moderate bleeding (*mild*).

B. **CRUSADE risk score** was estimated:

Predictor	Score
Baseline haematocrit %	
< 31	9
31–33.9	7
34–36.9	3
37–39.9	2
≥ 40	0
Creatinine clearance, ml/min	
≤ 15	39
> 15–30 35	
>30–60	28
>60–90	17
>90–120	7
>120	0
Heart rate (bpm)	
≤70	0
71–80	1
81–90	3
91–100	6
101–110	8
111–120	10
≥121	11
Sex	
Male	0
Female	8
Signs of congestive heart failure	
No	0
Yes	7
Prior vascular disease (peripheral artery disease or stroke)	
No	0
Yes	6
Diabetes mellitus	
No	0
Yes	6

Predictor	Score
Systolic blood pressure, mmHg	
≤90	10
91–100	8
101–120	5
121–180	1
181–200	3
≥201	5

The bleeding score is divided into quintiles: very low risk (≤20), low risk (21–30), moderate risk (31–40), high risk (41–50), and very high (>50).

2.1. Data collection

Data were enrolled using a standardized case report form. Patient collection data included demographic characteristics, medical history, presenting symptoms, biochemical and electrocardiographic findings, treatment practices either conservative or interventional, and a variety of bleeding data regarding location and amount of bleeding both in-hospital as well as during the next three months following presentation by phone call follow-up. Standardized definition of bleeding amount according to GUSTO bleeding score and patient-related variables of CRUSADE risk score were used. All cases with confirmed diagnosis of acute coronary syndrome were assigned to one of the following categories:

- ST-segment elevation myocardial infarction (STEMI),
- Non-ST segment elevation myocardial infarction (NSTEMI),
- Unstable angina.

For every Patient; the dose and duration of antiplatelet, antithrombotic, and thrombolysis was documented.

2.2. Statistical analysis

All statistical analyses were performed using SPSS for windows with statistical package version 15.0. Normally distributed continuous variables will be represented as mean ± SD, or as the percentage of the sample.

3. Results

– The current study data had included 823 patients, who were admitted to coronary care unit (CCU) of Ain Shams University hospital, Specialized Ain Shams hospital, and 6th of October insurance hospital during the period from 1/2014 till the end of 7/2014.

1. ***Demographic criteria of the study population:***

Among the studied patients, 630 (76.5%) were males, and 193 (23.5%) were females. Mean age among bleeders was 63 years compared with 57 years for non-bleeders. Mean body weight among bleeders was 78.86 kilograms compared with 86.35 kilograms for non-bleeders. As shown in Table 1, there were statistically significant differences between bleeders and non-bleeders regarding age, body weight.

2***. Risk factors profile of the study population:***

Among the studied patients, 395 (48%) of the patients were diabetic, compared with 428 (52%) of the patients were not diabetic. 55 (6.7%) of the patients had peripheral arterial disease or stroke (peripheral vascular disease), while 768 (93.3%) of the patients had no evidence of PAD (Table 2).

3. ***Clinical criteria of the study population:***

Among the studied patients, 54 (6.6%) of the studied patients had signs of congestive heart failure, compared with 769 patients who had no signs of heart failure. Mean systolic blood pressure on admission among the study population, was 140 mmHg. Mean heart rate on admission among the study population, was 88 bpm. There were no statistically significant differences between bleeders & non-bleeders regarding the admission heart rate, and the admission systolic blood pressure, as shown in Table 1.

4. ***Clinical presentation of the study population:***

Among the studied patients, 251 (30.5%) of the patients had presented with unstable angina, 401 (48.7%) had presented with NSTEMI, 171 (20.8%) of the studied patients had presented with STEMI.

5. ***Medictions received during hospitalization increasing bleeding tendency:***

All the studied patients had received DAPT in the form of acetyl-salicylic acid and clopidogrel. All of them had been anti-coagulated using either unfractioned heparin or LMWH (Enoxaparin). But, 82 (10%) of the patients had received glycoprotein IIbIIIa antagonists, compared with 741 (90%) of the patients who had not received this drug. And, only 26 (3.2%) of the patients had received thrombolytic therapy in the setting of STEMI either anterior or inferior.

6. ***Coronary interventions, results and recommendations (Table 3):***

26 (3.2%) of the patients did not undergo a diagnostic coronary angiogram, compared with 797 (96.8%) of the studied patients who had undergone coronary angiogram. Of whom, trans-femoral approach was performed in 780 patients (94.8%), compared with 17 patients (2.1%) who had coronary angiography performed using trans-radial approach. It was found that, 143 (17.4%) had either atherosclerotic coronary artery disease with no significant lesions or patent previously deployed stent/s, or patent grafts in post CABG patients.

- 374 (45.4%) of the patients had a single vessel disease LAD, LCX or RCA.
- 93 (11.3%) of the patients had two vessel disease, 142 (17.3%) of patients had multi-vessel disease or LM or both.
- 9 (1.1%) of the patients had cork screw vessels & 14 (1.7%) of the studied patients had ectatic vessels.
- 19 (2.3%) of the patients had in-stent restenosis of previously deployed stent/s.
- 2 (0.2%) of the patients had occluded venous grafts in status post CABG patients.
- With, only one patient had developed acute DES in-stent thrombosis.
- Regarding, the different recommendations for the studied patients, 181 (22%) of the patients had received medical treatment.
- 12 (1.5%) of the studied patients had received the traditional medical treatment of ischaemic heart disease in addition to warfarin.
- 146 (17.7%) of the patients had undergone CABG, with 197 (23.9%) had DES/s deployment, 272 (33%) had BMS/s deployment, with 12 (1.5%) had DES & BMS deployment.
- Only one patient had Redo-CABG, and one patient had undergone thrombus aspiration, and another one after thrombus aspiration, was kept on warfarin due to high thrombus burden.

7. ***Bleeding in different CRUSADE risk score subgroups, rate of bleeding, and sites of bleeding:***

A. ***Bleeding in different CRUSADE risk score subgroups:***

- Among the studied patients, 228 (27.7%) had very low risk for bleeding, of whom only 6.6% had experienced bleeding events.
- 268 (32.6%) had low risk, of whom 8.2% had experienced bleeding events.

Table 1
Comparison between bleeders and non-bleeders regarding selected quantitative variables.

	Bleeding							
	No Bleeding		Bleeding		Total			
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	t-test	p value
Age	57.05	8.02	63.05	9.21	58.49	8.70	8.845	<0.001
Weight	83.35	5.86	78.86	7.46	82.27	6.56	8.765	<0.001
Admission HR	87.22	9.34	88.54	11.31	87.54	9.86	1.639	0.102
Admission systolic Blood pressure	139.93	21.65	141.36	25.70	140.27	22.69	0.776	0.438
Baseline HCT	38.90	3.91	36.15	4.88	38.24	4.33	8.087	<0.001
S. creatinine	1.14	.29	1.32	.35	1.18	.31	7.434	<0.001
Creatinine clearance	87.15	24.74	64.52	21.92	81.70	25.95	11.519	<0.001

Table 2
Comparison between bleeders and non-bleeders regarding selected qualitative variables.

		No Bleeding		Bleeding		Total			
		No	%	No	%	No	%	Chi square	p value
Sex	Male	508	80.6	122	19.4	630	76.5	32.388	<0.001
	Female	117	60.6	76	39.4	193	23.5		
DM	N	368	86.0	60	14.0	428	52.0	49.197	<0.001
	Y	257	65.1	138	34.9	395	48.0		
Prior vascular disease	N	608	79.2	160	20.8	768	93.3	65.42	<0.001
	Y	17	30.9	38	69.1	55	6.7		
Signs of CHF	N	596	77.5	173	22.5	769	93.4	15.643	<0.001
	Y	29	53.7	25	46.3	54	6.6		
Presentation	UA	223	88.8	28	11.2	251	30.5	33.37	<0.001
	NSTEMI	285	71.1	116	28.9	401	48.7		
	STEMI	117	68.4	54	31.6	171	20.8		
DAPT	N	0	66.7	0	33.3	0	0	0.142	0.707
	Y	623	76.0	197	24.0	823	100		
Anti-coagulation	N	0	100.0	0	0.0	0	0	0.317	0.573
	Y	624	75.9	198	24.1	823	100		
Gb IIBIIIA	N	586	79.1	155	20.9	741	90.0	40.151	<0.001
	Y	39	47.6	43	52.4	82	10.0		
Thrombolytic	N	607	76.2	190	23.8	797	96.8	0.662	0.416
	Y	18	69.2	8	30.8	26	3.2		

Table 3
Description of the catheterization procedure in bleeders and non-bleeders and the whole group.

		No bleeding		Bleeding		Total	
		No	%	No	%	No	%
CA performed	N	24	92.3	2	7.7	26	3.2
	Y	601	75.4	196	24.6	797	96.8
Route of CA	No	24	92.3	2	7.7	26	3.2
	Fem	589	75.5	191	24.5	780	94.8
	Rad	12	70.6	5	29.4	17	2.1
CA performed	No	24	92.3	2	7.7	26	3.2
	ACAD, patent stents & or patent grafts	123	86.0	20	14.0	143	17.4
	Single vessel	289	77.3	85	22.7	374	45.4
	Two vessels	67	72.0	26	28.0	93	11.3
	Multiple disease	92	64.8	50	35.2	142	17.3
	Cork screw vessels	8	88.9	1	11.1	9	1.1
	Ectatic vessels	9	64.3	5	35.7	14	1.7
	In-stent- restenosis	12	63.2	7	36.8	19	2.3
	Occluded grafts	0	0.0	2	100.	2	0.2
	DES in-stent thrombosis	1	100.	0	0.0	1	0.1
Recommendations	Medical	157	86.7	24	13.3	181	22.0
	Medical+ Warfarin	8	66.7	4	33.3	12	1.5
	CABG	98	67.1	48	32.9	146	17.7
	DES	128	65.0	69	35.0	197	23.9
	BMS	227	83.5	45	16.5	272	33.0
	DES+BMS	6	50.0	6	50.0	12	1.5
	Redo-CABG	0	0.0	1	100.	1	0.1
	Thrombus aspiration	1	100.	0	0.0	1	0.1
	Thrombus aspiration +warfarin	0	0.0	1	100.	1	0.1
CRUSADE risk score	Very low	213	93.4	15	6.6	228	27.7
	Low	246	91.8	22	8.2	268	32.6
	Moderate	114	63.0	67	37.0	181	22.0
	High	43	43.4	56	56.6	99	12.0
	Very high	9	19.1	38	80.9	47	5.7

- 181 (22%) had moderate risk for bleeding, of whom, 37% had experienced bleeding events.
- 99 (12%) had high risk for bleeding, of whom 56.6% had experienced bleeding events.
- Very high risk for bleeding, had been found in 4 (5.7%) of the patients, of whom 80.9% had experienced bleeding events.

B. ***Absolute and relative risk of bleeding in the different levels of CRUSADE (Table 4):***

- The absolute risk (cumulative incidence) was 6.6% (95% CI 3.4–9.8%) in the group with the very low risk score and increased progressively to reach 80.85% (95% CI 69.6–92.1%) in the group of very high-risk score.
- Taking the absolute risk in the very low risk score as a reference, the relative risk in the subsequent risk score groups rises progressively to 1.3, 5.6, 8.6 and 12.3 in the low, moderate, high and very high-risk score subgroups respectively.

C. ***Absolute risk of mild and moderate bleeding in the different levels of the CRUSADE risk score (Table 5):***

- In either mild or moderate bleeding, the risk increased with an increasing risk score.
- Except in the very high-risk subgroup, the incidence of mild bleeding was higher than the incidence of moderate bleeding at each risk score subgroup. However, in the very high risk score subgroup the risk of moderate bleeding was 42.55% (95% CI 28.42–56.69%), higher than that for mild bleeding which was 38.3% ((% CI 24.4–52.2%).
- Among the patients who were at very low risk of bleeding based on CRUSADE risk score, 6.14% (14 patients) had experienced mild bleeding according to GUSTO classification, compared with 0.44% (1 patient) had experienced moderate bleeding according to GUSTO classification.
- Of those with low risk of bleeding, 7.84% (21 patients) had experienced mild bleeding; compared with 0.37% (1 patient) had experienced moderate bleeding.
- Of those with moderate risk of bleeding, 24.31% (44 patients) had experienced mild bleeding; compared with 12.71% (23 patients) had experienced moderate bleeding.
- Of those with high risk of bleeding, 31.31% (31 patients) had experienced mild bleeding; compared with 25.25% (25 patients) had experienced moderate bleeding.
- Of those with very high risk of bleeding, 38.30% (18 patients) had experienced mild bleeding, compared with 42.55% (20 patients) had experienced moderate bleeding.

D. ***Incidence of bleeding by site & bleeding sites of all cases (Table 6):***

- In general, bleeding at the puncture site was the most common, comprising more than half (53.5%) of the bleeders with an incidence of 12.88%. This was followed by bleeding from GIT, 24.7% of bleeders with incidence of 5.95%, followed by hematuria (5.6%) of the patients while bleeding per gums was the rarest, 3.5% of bleeders with incidence of 0.85%, followed by hematuria (5.6%) of the patients, followed by small numbers of bleeding per gums & hemoptysis and combination of puncture site and hematuria.

8. ***Comparison between bleeders and non-bleeders regarding selected qualitative variables:***

A. *Sex*

- 39.4% of females had experienced bleeding events, compared with 19.4% of male sex category, it was statistically significant (P value < 0.001).

B. *Risk factors profile*

- 34.9% of diabetic patients had experienced bleeding events compared with 14.0% of non-diabetic patients, this was statistically significant (p value < 0.001).
- 69.1% of those with prior vascular disease had experienced bleeding events, compared to 20.8% of those without prior vascular disease. This was statistically significant (p value < 0.001).

C. *Presentation:*

11.2% of unstable angina patients had experienced bleeding events, compared to 28.9% of NSTEMI patients & 31.6% of STEMI, reflecting increased bleeding events with severity of presentation. This was statistically significant (P value < 0.001).

D. *Clinical data:*

- 46.3% of those with signs of congestive heart failure had developed bleeding events, compared to 22.5% of those without signs of congestive heart failure. This was statistically significant (P value < 0.001).

E. *Medications:*

52.4% of those received glycoprotein IIb/IIIa antagonists had experienced bleeding events, compared with 20.9% of those who did not receive these drugs. This was statistically significant (p. value < 0.001). Among the different anti-thrombotic medications, the use of this medication was the only statistically significant drug.

4. Discussion

The CRUSADE bleeding score, which predicts baseline risk of in-hospital major bleeding, was developed and validated in >89,000 community-treated NSTEMI patients. It considers only admission baseline characteristics, clinical presentation, and laboratory data. The 8 variables in the final model were female sex, history of diabetes, prior vascular disease, heart rate, systolic blood pressure, signs of CHF, baseline HCT < 36%, and creatinine clearance. CRUSADE bleeding score demonstrated preserved discrimination across treatment subgroups.[10]

Table 4
Absolute and relative risk of bleeding in the different levels of the CRUSADE risk score.

CRUSADE risk score	Total	Incidence of bleeding		95 CI of incidence			95 CI of RR	
		No	%	LCL	UCL	RR	LCL	UCL
Very low	228	15	6.60	3.40	9.80	1	–	–
Low	268	22	8.21	4.90	11.50	1.2	0.7	2.3
Moderate	181	67	37.02	30.00	44.10	5.6	3.3	9.9
High	99	56	56.57	46.80	66.30	8.6	5.1	14.4
Very high	47	38	80.85	69.60	92.10	12.3	7.4	20.4
Total	823	198	24.06	21.26	27.09	–	–	–

Table 5
Absolute risk of mild and moderate bleeding in the different levels of the CRUSADE risk score

CRUSADE risk score	Total	Mild bleeding				Moderate bleeding			
		Incidence		95 CI of incidence		Incidence		95 CI of incidence	
		No	%	LCL	UCL	No	%	LCL	UCL
Very low	228	14	6.14	3.02	9.26	1	0.44	0.10	2.40
Low	268	21	7.84	4.62	11.05	1	0.37	0.10	2.10
Moderate	181	44	24.31	18.06	30.56	23	12.71	7.86	17.56
High	99	31	31.31	22.18	40.45	25	25.25	16.69	33.81
Very high	47	18	38.30	24.40	52.20	20	42.55	28.42	56.69

Table 6
Incidence of bleeding by site at different levels of CRUSADE risk score.

Site of bleeding	CRUSADE risk score											
	Very low		Low		Moderate		High		Very high		Total	
	No	%	No	%	No	%	No	%	No	%	No	%
Puncture site	13	1.58	16	1.94	36	4.37	26	3.16	15	1.82	106	12.88
GIT	2	0.24	2	0.24	15	1.82	17	2.07	13	1.58	49	5.95
Hematuria	0	0.00	3	0.36	4	0.49	3	0.36	1	0.12	11	1.34
Puncture site + GIT	0	0.00	0	0.00	6	0.73	5	0.61	6	0.73	17	2.07
Hemoptysis	0	0.00	0	0.00	1	0.12	0	0.00	1	0.12	2	0.24
Puncture site + Hematuria	0	0.00	0	0.00	1	0.12	3	0.36	2	0.24	6	0.73
Bleeding per gums	0	0.00	1	0.12	4	0.49	2	0.24	0	0.00	7	0.85

Bleeding is a common complicating issue following management of NSTEMI, with important immediate and late clinical consequences and with a 5-fold increase in 30-day mortality.[10]

Reduction in bleeding is reflected into improved survival. Prevention of major bleeding may represent an important step in improving results by balancing efficacy and safety in management of NSTEMI.[14–16]

The current study had classified bleeding according to GUSTO classification of bleeding into severe or life threatening (either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention), moderate (bleeding that requires blood transfusion but does not result in hemodynamic compromise), mild (bleeding that doesn't meet criteria for either severe or moderate bleeding).[17,18]

In the CRUSADE study published in circulation 2009, authors had demonstrated that in 71,277 patients who were included, very low risk CRUSADE were (≤20; n = 19,486) in whom 3.1% had experienced major bleeding, low risk (21–30; n = 12.545) 5.6% had experienced major bleeding, moderate risk (31–40; n = 11,530) 8.6% had experienced major bleeding, high risk (41–50; n = 10,961) 13.4% had experienced major bleeding, and very high risk (>50; n = 15,210)22.6% had experienced major bleeding.[14]

In the current study, 823 patients had been included, very low risk (n = 228), low risk (n = 268), moderate risk (n = 181), high risk (n = 99), very high risk (n = 47). Among those with very low risk, 6.14% had experienced mild bleeding and 0.44% had experienced moderate bleeding. Those with low risk, 7.84% had experienced mild bleeding and 0.37% had experienced moderate bleeding. With moderate risk, 24.31% had experienced mild bleeding, compared with 12.71% had experienced moderate bleeding. With high risk, 31.31% had experienced mild bleeding, compared with 25.25% had experienced moderate bleeding. With very high risk based on CRUSADE risk score, 38.30% had experienced mild bleeding, compared with 42.55% had experienced moderate bleeding based on GUSTO classification.

In the CRUSADE study, the authors had determined that CRUSADE patients had a median age of 67 years, were 60%males, and 40% females, with occurrence of intracranial hemorrhage (0.7%), documented retroperitoneal bleeding (1.9%), HCT drop (44.4%), patients with major bleeding had higher rates of in-hospital heart failure (15.9% vs. 6.5%), higher heart rate, lower body weight, lower systolic blood pressure, were older in age, lower baseline haematocrit, lower creatinine clearance. While in the current study, 76.5% of the studied patients were males, and 23.5% were females. Statistically significant differences had been noticed between bleeders and non-bleeders, Bleeders were older (mean age 58 years), had less body weight, had lower HCT value, were more renally impaired. Also more bleeding had been noticed among female sex category, among diabetic patients, history of previous vascular disease and presence of signs of congestive heart failure on clinical examination on admission, as well as administration of glycoprotein IIb/IIIa antagonists with no statistically significant differences regarding admission heart rate and blood pressure between the two groups.

In the CRUSADE study, the rates of major in-hospital bleeding across the quintiles of risk groups were 3.1% (very low risk), 5.5% (low risk), 8.6% (moderate risk), 11.9% (high risk), and 19.5% very high risk. Regarding the current study, the incidence (absolute risk) of bleeding among different risk group quintiles was 6.6% (very low), 8.21% (low risk), 37.02% (moderate risk), 56.57% (high risk), 80.85% (very high risk). In either mild or moderate bleeding, the bleeding increased with increasing the risk score.

In the CRUSADE study, the rate of major in-hospital bleeding was higher in those subjected to invasive approach as compared to conservative approach. In the current study, 797 patients had undergone a diagnostic coronary angiogram with or without PCI, and 26 were subjected to conservative strategy, with bleeding events either mild or moderate, 24.6% among invasive strategy, or 7.7% among conservative strategy.

In the GRACE registry, Moscucci et al. determined predictors of bleeding among 24,045 STEMI & NSTEMI patients, similar to the current results, They observed that female sex, renal insufficiency were independent predictors of major bleeding, but un-like the current results, they had observed that blood pressure was independent predictor of major bleeding.

Pharmacological interventions including diuretics, inotropic gents, thrombolytic agents, glycoprotein IIb/IIIa antagonists, and vasodilators were found to be independently associated with an increased risk of bleeding. Similarly, the use of right heart catheterization and PCI were independently associated with increased risk

of bleeding. The predictive factors for major bleeding were similar among the subgroups of patients who presented with STEMI (4.8%), NSTEMI (4.7%), or unstable angina (2.3%).

Spencer et al. also had found that female sex category, peripheral artery disease, renal insufficiency were among the predictors of major bleeding in the first 30 days after admission in GRACE registry, similar to the current results. But, unlike the current results, they had noticed that heart rate was among predictors of major bleeding although, it was statistically insignificant in the current study results.[17,20,21]

Regarding the clinical presentation, there appears to be a trend towards increased bleeding risk with increasing presentation severity, which is higher for ACS, and highest for STEMI. In urgent and elective PCI, Thrombolysis in Myocardial Infarction (TIMI) major bleeding occurred in 0.7% of the 6010 patients from the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events–2 (REPLACE-2) trial. The REPLACE-2 trial classified bleeding as major and minor based on both adverse clinical events and laboratory values. Independent baseline predictors of major hemorrhage included advanced age, female gender, impaired creatinine clearance, and anemia (defined using

World Health Organization criteria of hemoglobin 13 g/dl in men and 12 g/dl in women) whereas independent periprocedural predictive factors had included treatment with heparin plus Glycoprotein IIb/IIIa antagonists, increased procedural duration, provisional use of Glycoprotein IIb/IIIa antagonists, increased time to sheath removal, length of intensive care unit stay, and use of an intra-aortic balloon pump. Finally, REPLACE-2 reported significantly higher rates of protocol-defined major bleeding in patients with baseline anemia (4.9% vs 2.8%, P = 0.0001).[22,23]

Nikolasky et al., similar to the current results, had found that female sex, baseline anemia, and lower creatinine clearance were independent predictors of bleeding.

In NST-ACS, TIMI major bleeding occurred in 1.5% of the 13,819 patients from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. Gastrointestinal bleeding within 30 days of randomization had occurred in 178 patients (1.3%), including 107 of 7,789 (1.4%) patients triaged to PCI, 28 of 1,539 (1.8%) patients triaged to CABG and 43of 4.491 (1.0%) patients triaged to medical treatment. Rates of gastrointestinal bleeding were the highest in patients randomized to heparin plus glycoprotein IIb/IIIa antagonists (1.5%) followed by bivalirudin plus glycoprotein IIb/IIIa antagonists (1.4%) and bivalirudin monotherapy (0.9%). The incidence of gastrointestinal bleeding had increased with age from 0.57% in patients ≤50 years of age to 0.95%, 1.13%, 1.87%, and 3.54% in patients (>50 to ≤60), (>60 to ≤70), (> 70 to ≤80), and (>80) years of age respectively. Patients who developed gastro- intestinal bleeding were older and more frequently female, and had higher rates of diabetes mellitus, including a higher prevalence of insulin-treated diabetes, worse renal function and anemia. Gastro-intestinal bleeding was the second most frequent source of non-CABG- related bleeding after access- site bleeding and was the most common source of bleeding among patients triaged to medical management. Nikolsky et al. also noted increased bleeding rates in patients with anemia undergoing PCI (11.5% vs 8.1%, P = 0.0001).[24–26]

Park et al. showed that regardless of vascular access, the incidence of bleeding was also higher among the CRUSADE highest risk groups in Korean patients. The rate of bleeding complication seemed to be more prevalent in patients with ACS or AMI than those with stable angina. Initial diagnosis as NSTEMI, hematocrit < 31%, use of glycoprotein IIb/IIIa inhibitors, and history of hypertension were also significant predictors of in-hospital major bleeding. However, trans-radial intervention was a negative predictor. Bleeding complications after PCI are most commonly related to vascular access site, trans-radial intervention was associated with a significant reduction in in-hospital major bleeding that was more prominent in patients with high-risk subgroups, such as patients more than 65 years old, history of hypertension and diabetes, low left ventricular ejection fraction, impaired renal function, NSTEMI and high- to very high-bleeding risk. In the current study, 29.4% of those who had trans-radial interventions had experienced bleeding events compared with 24.5% of trans-femoral interventions.[27]

In STEMI patients, TIMI major bleeding occurred in 4.1% of the 3,602 patients with STEMI from the Harmonizing Outcomes with Revascularization and Stents (HORIZONS) trial. Results from the HORIZONS-AMI consisting of 3602 STEMI patients undergoing primary PCI who were randomized to receive bivalirudin monotherapy and provisional glycoprotein IIb/IIIa antagonists or heparin plus glycoprotein IIb/IIIa antagonists demonstrated that bivalirudin monotherapy had resulted in significantly reduced 30-day rates of major bleeding and net adverse clinical events (9.2% versus 12.1%; relative risk [RR] 0.76, $P = 0.005$), compared with heparin plus GPI (abciximab or eptifibatide) owing to a lower rate of major bleeding (4.9% versus 8.3%, respectively, P, 0.001). Similarly, 30-day rates of death from cardiac causes (RR 0.62, $P = 0.03$) and death from all causes (RR0.66, $P = 0.047$) were lower in the patients who received bivalirudin alone, compared with their counterparts treated with heparin plus glycoprotein IIb/IIIa antagonists. The safety and efficacy of bivalirudin monotherapy compared with heparin plus glycoprotein IIbIIIa antagonists were sustained at three years follow-up.[7,28,29]

In the current study, 11.2% of unstable angina patients had experienced bleeding events compared with 28.9% among NSTEMI, and 31.6% among STEMI patients.

In the setting of ACS, patients with anemia were more vulnerable to bleeding than their counterparts without anemia. In CADILLAC, patients with baseline anemia had a higher rate of in-hospital hemorrhagic complications (6.2% vs 2.4%, p < 0.002).[23]

The OASIS-5 trial demonstrated that fondaparinux was similar to enoxaparin in reducing the risk of ischemic events in patients with non-ST elevation ACS at nine days while substantially reducing the risk of major bleeding.[30]

In the current study increased bleeding rates were higher in anemic patients (lower HCT values) in comparison to normal baseline HCT Level at admission with significant P-value (p < 0.001). Also, fondaparinux wasn't used in the current study.

Aggressive anti-thrombotic and antiplatelet therapies may contribute to increased hemorrhagic complication rates in patients with anemia undergoing PCI for ACS and STEMI. In the Global Registry of Acute Coronary Events (GRACE), 23.8% of bleeds were at vascular access sites, (18.6% vs 5.1%, p = 0.001). In comparison to the current study, bleeding at the puncture site was the most common compromising more than half of the bleeders (53.5%) with incidence of 12.88% followed by bleeding from GIT (24.7%) with incidence of 5.95%, while bleeding per gums were the rarest, (3.5%) of the bleeders with incidence of 0.85%. However, the definition of Major bleeding in the Global Registry of Acute Coronary Events (GRACE) study (Requiring a transfusion of ≥2 Units Packed RBCs, Resulting in a decrease in hematocrit of ≥10%, Intracerebral haemorrhage or hemorrhage resulting in death or stroke) was different from the GUSTO bleeding classification used in the current study.[21,28]

Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial investigators revealed that in patients with NSTE ACS, reduction in ischemic complications was associated with significantly greater major (3.7% vs 2.7%, P = 0.001) and minor (5.1% vs 2.4%, P = 0.001) bleeding events, with most bleeds occurring at vascular access sites and in the gastrointestinal tract. Dual inhibition of platelet aggregation decreases the incidence of ischemic events; however, these benefits must be weighed against the increased

risk of major bleeding in ACS patients, particularly those with anemia. Among ACS patients, adding clopidogrel to aspirin was associated with an absolute 0.2% to1.0% increase in major bleeding. However, the statistical significance of this increased bleeding varied among the trials.

There were 3 specific groups at increased risk for bleeding with thienopyridines:

(1) patients $\geq$ 75 years of age,
(2) patients with previous stroke/transient ischemic attack,
(3) patients weighing $\leq$ 60 kg.[11,12]

In comparison to the current study, administration of dual antiplatelet therapy had no statistically significant differences between bleeders and non-bleeders.

Kjaer et al. study had demonstrated increased risk of major bleeding in un-selected patients receiving combination therapy with aspirin and clopidogrel in patients presented with unstable angina or NSTEMI, with major bleeding complications most frequently occurring in patients above 70 years of age and following bypass surgery, un like the current study, that had demonstrated no statistically significant differences between bleeders and non-bleeders receiving DAPT.[19]

David et al. had demonstrated a small but significant increased incidence of bleeding most commonly at vascular access site in patients had been administered glycoprotein IIb/IIIa antagonists. In a meta-analysis, glycoprotein IIb/IIIa antagonists use in UA/NSTEMI patients was associated with a significant excess of major bleeding complications (2.4% vs 1.4%, $P < 0.0001$), although intracranial bleeding was not increased significantly.[13]

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