Validation of a Score for Predicting Bleeding Events during Acute Coronary Syndromes

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Abstract

Background: Bleeding is a major complication in patients treated for acute coronary syndromes (ACS) with antithrombotic and invasive therapies. Consequently, the benefit of such therapies should be balanced against the potential risk of hemorrhagic complications. Therefore, a score to estimate individual risk of bleeding might represent an important tool in clinical decision-making.

Objective: This study aims to create and validate a bleeding risk score for patients with ACS.

Methods: Independent predictors of bleeding reported by the GRACE Registry were utilized. Variables with odds ratio (OR) ≥ 2.5 in that Registry added 3 points (previous history of bleeding), OR = 1.5-2.4 added 2 points (creatinine clearance < 30 ml/min, female gender) and those with OR < 1.5 added 1 point (clearance between 30 and 60 ml/min, each 10 years of age > 30, ST-deviation, peripheral artery disease and smoking). The score was validated in a cohort of 383 individuals with ACS. In-hospital bleeding was defined as hematocrit fall ≥ 10%, blood transfusion ≥ 2 units, intracerebral bleeding or fatal bleeding.

Results: The incidence of bleeding events was 3.1% and the score's C-statistics was 0.66 (95% CI = 0.52-0.80), indicating a predictive ability towards these events. Those with a score ≥ 7 had 6% incidence of bleeding, compared with 1.9% if the score was < 7 (RR = 3.2; 95%CI = 1.04-9.9; p = 0.03). There was an interaction between a score ≥ 7 and greater risk imposed by treatment with Clopidogrel (p = 0.02), IIb/IIIa blockers (p = 0.06) and surgical revascularization (p < 0.001).

Conclusion: The score discriminates bleeding risk and is potentially useful in clinical decision-making during ACS. (Arq Bras Cardiol 2010; 95(4): 457-463)

Key words: Hemorrhage; risk; acute coronary syndrome.

Introduction

Acute coronary syndromes (ACS) are associated with significant rates of recurrent ischemic events in the short[1,2] and long-term[3]. To reduce the chance of recurrent events, antithrombotic therapy and invasive procedures are indicated, at the expense of increasing the risk of bleeding complications[4,5]. In this context, independent predictors of bleeding have been reported by several studies[6-9]. In order to apply this knowledge to clinical practice, these predictors can be used to create a score that allows physicians to estimate individual risk of bleeding.

Some facts suggested that a bleeding score would be useful in clinical decision-making during ACS. Bleeding is associated with a significant rise in mortality, varying from 6% to 17% of absolute increase in short-term death according to different studies[7-9]; the very same treatments (antithrombotic therapy and invasive coronary procedures) intended to prevent recurrent ischemic events, paradoxically increase the incidence of bleeding[4,5]. Finally, the withdrawn of antithrombotic therapy during bleeding events enhances patients vulnerability to ischemic events[9]. Therefore, it is important to compare the risk of ischemic events and the risk of bleeding events in each individual, in order to define how aggressive the treatment should be. For instance, those with low bleeding-risk and high ischemic-risk should benefit from aggressive antithrombotic therapy, while those with high bleeding-risk and low ischemic-risk should not receive intense antithrombotic therapy.

The present study created and tested a score to estimate the chance of bleeding complications in individuals admitted with ACS. The score was built based on previous literature regarding bleeding predictors and was validated in a local cohort of patients hospitalized with unstable angina, non-ST or ST-segment elevation acute myocardial infarction.

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Methods

Sample selection

Consecutive patients with acute coronary syndromes, at least 18 years of age, admitted in the coronary care unit of our Hospital between 1999 and 2007 were considered candidates for the study. Inclusion criteria were defined as chest pain or equivalent within 24 hours of admission and at least one of the following characteristics: 1) electrocardiographic ischemic changes, defined as dynamic T wave inversion, ST-segment depression or ST-segment elevation; 2) elevation of serum markers of myocardial necrosis; 3) previous documentation of coronary artery disease. All participants provided written informed consent and the protocol was approved by the Institution's human research ethic committee.

Bleeding score

To create the bleeding score, published data regarding predictors of bleeding in the GRACE registry were utilized[9]. Based on that registry, the independent predictors of bleeding were included in the score, according to the following rule: 1 point if the odds ratio was < 1.5 in the Registry, 2 points if the odds ratio was between 1.5 and 2.4, and 3 points when the odds ratio was ≥ 2.5. Since it was intended to be an admission score, only variables typically available at admission were considered. Thus, the score consisted of the following variables: history of bleeding (3 points), creatinine clearance < 30 ml/min (2 points), creatinine clearance = 30 - 59 ml/min (1 point), female gender (1 point), peripheral artery disease (1 point), smoking (1 point) and ST-segment deviation (1 point) and each decade of age older than 30 years old (1 point). Creatinine clearance was calculated according to the Cockcroft-Gault formula[10].

Endpoint sefinition

Clinically manifested hemorrhages were defined as a bleeding event for the present analysis when at least one of the major criteria was present: hematocrit fall ≥ 10%, transfusion requirement ≥ 2 units, cerebral hemorrhage or fatal hemorrhage[9]. Thus, only major bleeding events were taken into consideration. Recurrent ischemic events during hospitalization were defined as the composite of nonfatal acute myocardial infarction or recurrent unstable angina. Myocardial infarction as an outcome endpoint was defined as either a new Q-wave or troponin elevation during hospitalization despite normal values during the first 24 hours. For patients with infarction at admission, a new peak of mass CK-MB (> 50% the previous value and above the normal value) was required for diagnosis of reinfarction. An episode of rest angina was recorded as recurrent unstable angina if one of the following criteria was present: physician decision to administer sublingual nitrates or initiate intravenous nitrates, dynamic electrocardiographic changes and physician decision to perform emergency coronary angiography. In-hospital death was also recorded as a cardiovascular endpoint.

Data analysis

The discriminatory ability of the bleeding score was tested by C-statistics, defined as the area under the receiver operator characteristic (ROC) curve, and calibration (observed vs. predicted risk) was assessed by Hosmer-Lemeshow statistic. Based on the ROC curve, the most accurate cut-off point for bleeding prediction was identified. Then, individuals were dichotomized according to this cut-off and incidence of bleeding compared between the two groups, by Chi-square test. In addition, the incidence of bleeding was compared among the three tertiles of the bleeding score and p for trend was obtained through linear-by-linear Chi-square test. In order to evaluate whether the association between the score and bleeding events depended on treatment strategies acting as confounding variables, pharmacologic and invasive treatments were compared between the groups dichotomized by the score, using Chi-square test. Moreover, logistic regression analysis was used to evaluate interaction between the bleeding score and treatment.

The GRACE score for in-hospital mortality was calculated for all patients[11]. Spearman's correlation coefficient was utilized to test the association between the GRACE score and the bleeding score. Then, the GRACE score was dichotomized using the cutoff of 141, which defines high-risk individuals according to previous literature[11]. Finally, in-hospital death and recurrent ischemic events were compared between individual with bleeding events and those free of hemorrhage by Chi-square test.

Ordinal variables (scores) were expressed as medians (interquartile range) and continuous variables as means and standard deviation. For baseline characteristics analysis, continuous variables were compared between two groups by Student's *t* test and categorical variables by Chi-square test. When expected values in the association of two categorical values were < 1, Fisher's exact test was used instead of Chi-square test. The SPSS software package release 10.0 was used for data analysis and a p value < 0.05 was considered statistically significant.

Results

Sample population

Three hundred and eighty-three patients were studied, aged 66 ± 12 years old, 42% females, 21% admitted with ST-segment elevation infarction, 29% with non-ST elevation infarction and the remaining with unstable angina. The incidence of major bleeding during hospitalization was 3.1%. The GRACE Score for in-hospital mortality had a median of 111 (interquartile range: 92 - 133), indicating that half of the patients were considered at least intermediate risk for ischemic complications (GRACE Score > 109). Clinical characteristics are depicted on Table 1.

Predictive ability of the bleeding score

The bleeding score had a median of 5 (interquartile range: 4 - 7). Considering the components of the score, creatinine clearance between 30 and 60 ml/min, female gender and ST-segment deviation were the most prevalent, peripheral artery disease and smoking were less frequent (< 20% each), while previous bleeding and clearance < 30 ml/min were

Table 1 - Baseline characteristics of sample population

Variable	Numeric description
Sample size	383
Age (years)	66 ± 12
Female gender	160 (42%)
Weight (kg)	72 ± 14
Body mass index (kg/m²)	26 ± 4.2
ST-elevation myocardial infarction	80 (21%)
ST-deviation on EKG	170 (44%)
Previous bleeding	4 (1%)
Creatinine at admission (mg/dl)	1.15 ± 0.73
Left ventricle EF < 45%	(68/354) 19%
Triple-vessel or left main disease	73 (19%)
Diabetes	112 (29%)
Hypertension	295 (77%)
Smoking	66 (17%)
Total cholesterol (mg/dl)	200 ± 45
Triglycerides (mg/dl)	144 ± 90
Previous coronary artery disease	212 (55%)
Peripheral artery disease	21 (5.5%)
Cerebrovascular disease	18 (4.7%)
Grace mortality score	111 (92 – 133)

EF - ejection fraction in patients who underwent echocardiogram. A Grace risk score range of 99 - 140 is considered intermediate risk (1-3% hospital mortality)[11].

rare (< 3%) - Table 1. The score's C-statistics was 0.66 (95% CI: 0.52 - 0.80), indicating a significant prediction of bleeding events during hospitalization - Figure 1. The point presenting the best predictive accuracy was 7, and the incidence of in-hospital major bleeding in individuals with a score ≥ 7 was 6%, compared with 1.9% in those with a score < 7 (relative risk = 3.2; 95% CI = 1.04 - 9.9; p = 0.03). When the sample population was divided into tertiles of the bleeding score, the incidences in the first, second and third tertiles were progressively higher (1.6%, 2.7% and 6%, respectively; p for trend = 0.03). The Hosmer-Lemeshow p value for the score was 0.49, indicating good calibration.

Major bleeding and treatment approach according to the score

Pharmacological and interventional treatments were similar between the groups of score ≥ 7 and < 7, indicating that the predictive ability of the score was independent from the established treatment - Table 2. To evaluate whether the association between bleeding events and antithrombotic or invasive treatment was modified (or predicted) by the score, interaction terms were calculated by logistic regression. Interaction between treatment and score ≥ 7 was significant for Clopidogrel (p = 0.02) and surgical revascularization (p < 0.001) and a trend was observed with GP IIb/IIIa receptor blockers (p = 0.06). Indeed, only individuals with a score ≥ 7 experienced bleeding increase with these drugs - Figure 3. Seemingly, compared with non-surgical patients, surgery was associated with a 15-fold increase in bleeding events in individuals with a score ≥ 7, while the increase was only 3-fold if the patient had a score < 7 - Figure 2. Conversely,

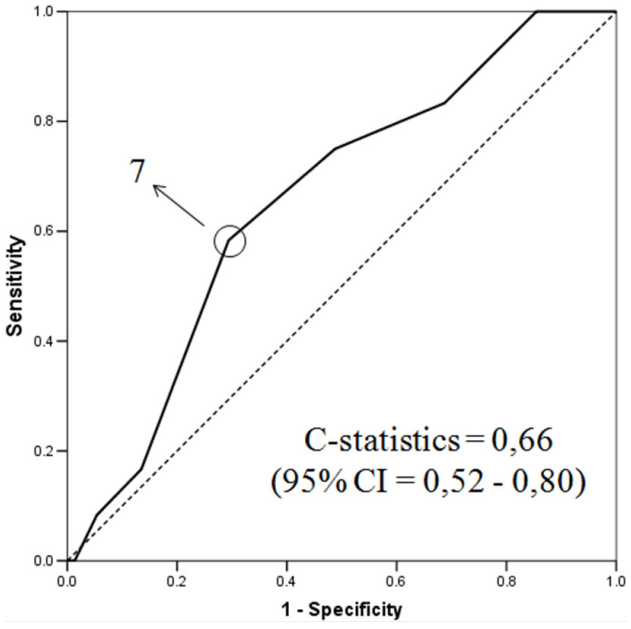

Figure 1 - ROC curve analysis of the bleeding score in relation to in-hospital major bleeding. The number seven indicates the cut-off point value of best accuracy.

there was no score interaction with thrombolytic therapy (p = 0.16) and angioplasty (p = 0.23).

Relationship between bleeding prediction and ischemic death

When the bleeding risk is different from the ischemic risk, there is a clear-cut definition of the best approach in relation to anti-ischemic therapies that increase bleeding events. Thus, it is important to evaluate the bleeding score in relation to the GRACE score. There was a significant positive correlation between the bleeding score and the GRACE score for in-hospital mortality (R = 0.59; p < 0.001) - Figure 3. Sixty-one percent of patients were defined as presenting both low risk of bleeding (score ≥ 7) and low risk of ischemic death (GRACE score ≥ 140), while 11.5% were classified as high-risk by both scores. Conversely, the two scores disagreed in 28% of individuals, 18% were defined as presenting high risk of bleeding and low risk of ischemic death and 9.5% as presenting low risk of bleeding and high risk of ischemic death - Figure 2.

Table 2 - Comparison of antithrombotic drugs and interventional procedures between bleeding risk groups

	Bleeding score < 7	Bleeding score ≥ 7	p value
Number	267	116	
Aspirin	251 (94%)	103 (89%)	0.06
Clopidogrel	156 (58%)	62 (53%)	0.31
LMW heparin	243 (91%)	104 (90%)	0.60
UF heparin	7 (2.6%)	5 (4.3%)	0.40
GP IIb/IIIa blocker	37 (14%)	17 (15%)	0.86
Thrombolytic	23 (8.6%)	8 (6.9%)	0.56
Coronary angiography	196 (73%)	87 (75%)	0.79
Coronary angioplasty	119 (45%)	50 (43%)	0.77
CABG surgery	17 (6.4%)	5 (4.3%)	0.42
Previous aspirin	107 (40%)	44 (38%)	0.67
Previous warfarin	6 (2.2%)	0	0.18

LMW - low molecular weight; UF - unfractionated; CABG - coronary artery bypass graft.

Bleeding as a risk factor for ischemic events

Individuals who experienced major bleeding events during hospitalization had a higher incidence of recurrent ischemic events, in relation to those free of hemorrhage (50% *vs* 23%, p = 0.03). In accordance, in-hospital death was more frequent in individuals with major bleeding (25% *vs* 3.5%, p = 0.01).

Discussion

The present study proposed a score to estimate the risk of bleeding in individuals hospitalized with ACS. The score presented a reasonable performance regarding discrimination and a good calibration, as individuals with a score ≥ 7 had a 3-fold higher incidence of bleeding events. Moreover, the interaction analysis showed that the score was able to discriminate individuals that were vulnerable to therapy-related bleeding.

Compared to well-validated risk scores, the discriminatory

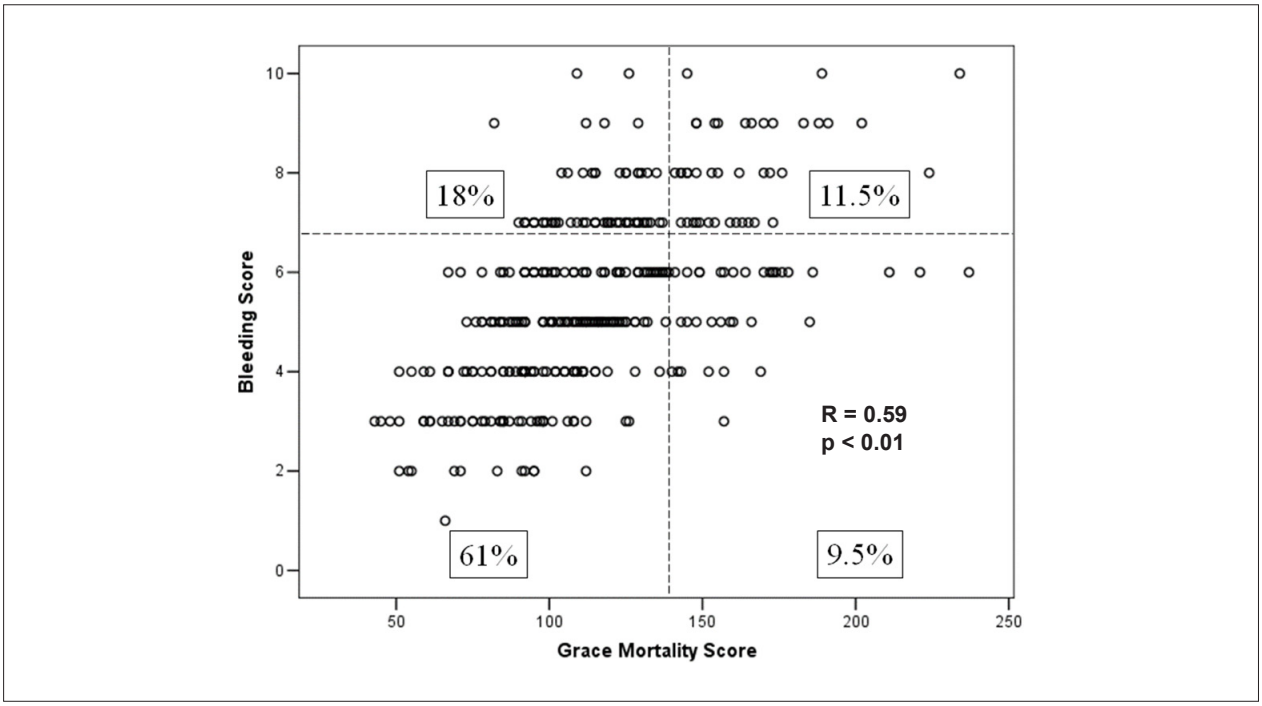

Figure 2 - Scatter plot of the correlation between Grace mortality score and bleeding score. Horizontal dashed line divides individuals as bleeding score ≥ 7 or < 7. Vertical dashed line divides individuals as Grace score ≥ 141 (high risk group). Percentages mean the frequency of individuals in each quadrant determined by the dashed lines.

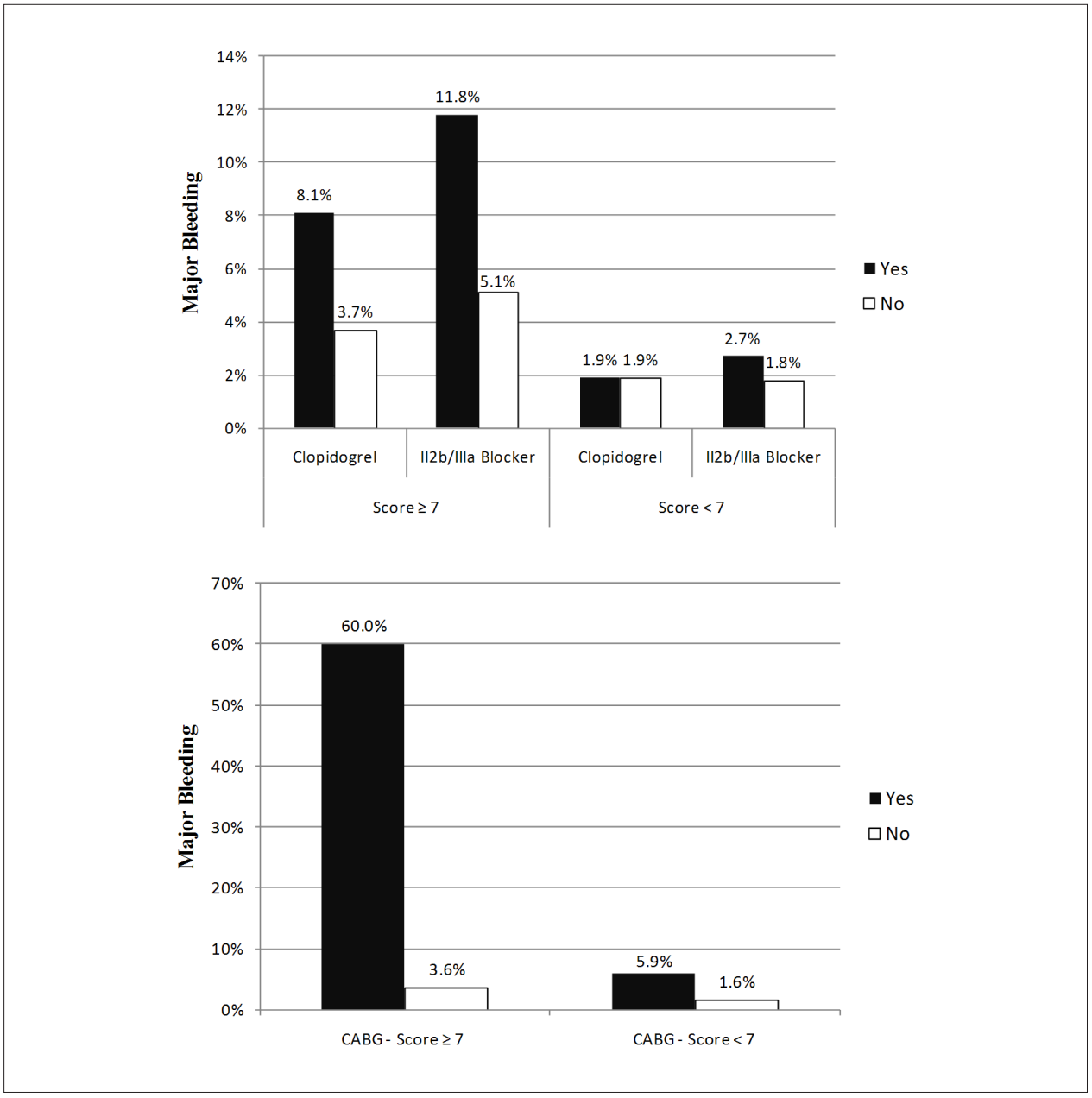

Figure 3 - Comparison of major bleeding incidence between individuals who utilized and did not utilized Clopidogrel, IIb/IIIa blockers and CABG surgery, stratified by bleeding score ≥ 7 or < 7.

ability of the present score, measured by a C-statistics of 0.66, should be considered acceptable. For instance, a recently validated score for the prediction of bleeding during percutaneous coronary intervention was considered useful based on a C-statistics of 0.62[12]; the TIMI-Risk Score has a C-statistics of 0.68 for mortality in ACS; and the C-statistics of the Framingham Score varies between 0.65 and 0.85 according to the population studied[13,14]. On the other hand, further studies are necessary to identify new predictors capable of improving the current ability of the bleeding score.

A direct correlation between the bleeding score and the GRACE ischemic mortality score was observed, probably due to common variables between the two, such as age, renal function and ST-deviation. Regardless of that, according to these scores, about one-third of the patients presented a high risk of bleeding with a low risk of ischemia or vice-versa. The scores present a clear-cut definition of risk-benefit for these patients. For the remaining patients, more elaborate decision trees should be used based on the scores' risk estimation.

In the present study, the bleeding incidence of 3.1% was similar to what has been reported in different cohorts[6-9,15,16], indicating the external validity of our sample population. Studies differ in relation to major bleeding definitions. Some are conservative and define major bleeding depending

only on clinical manifestation, such as the GUSTO criteria. Others are more liberal and use laboratory criteria together with clinical criteria[17]. We chose to define major bleeding by both clinical (fatal, cerebral hemorrhage or need for transfusion) and laboratory criteria (hematocrit fall > 10%), as this definition of bleeding is more sensitive to detect this undesirable complication.

Several studies have reported independent predictors of bleeding[6-9,15,16]. We chose to use the data provided by the GRACE registry[9], because it was the largest cohort to report such results and it is a pure observational registry, as opposed to some cohorts originated from clinical trials[6,7]. Despite some variation among studies, in general the cohorts provide similar results regarding predictors. These studies have reported antithrombotic and invasive treatments as predictors of bleeding. However, we chose not to include treatment variables in score calculation, because as a clinical tool, it is more useful to determine baseline risk at admission, before treatment choices have been made.

Study limitations should be recognized. Our sample was large enough to provide a sufficient certainty that the results were not driven by chance, but the frequency of bleeding events in each subgroup defined by the score should not be seen as a precise estimation, because of limited sample size. For instance, we reported that a high-risk score implies a chance of 6% in bleeding. However, the 95% confidence interval for this incidence is 2.7% to 12%. In this regard, larger studies are necessary to better quantify absolute risk related to score results. Secondly, due to the small sample size, we could not stratify individuals into more than three groups of risk. The score will be more useful if it stratifies patients in several groups of bleeding risk, with a wider range of risk variation and much greater risk in the extremities. In other words, when larger samples are studied, subgroups of higher risk than 6% will be identified. Thirdly, although the beneficial effect of the score is very plausible, the efficacy of the score in clinical decision-making remains to be proved by randomized clinical trials.

Conclusion

The present study validates a score to determine bleeding risk during hospitalization for ACS and suggests the use of this tool as a means to optimize therapeutic decisions targeted to reduce ischemic events.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

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