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Comparison of Different Bleeding Risk Scores to Predict in-Hospital Major Bleeding in Patients with Acute Pulmonary Embolism who Underwent Thrombolytic Treatment

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ABSTRACT

Objective: Certain bleeding risk scores have been proposed to predict major bleeding (MB) events in patients with acute pulmonary embolism (APE) during anticoagulation therapy. Since patients who undergo thrombolytic treatment are usually excluded from such studies, it is unknown whether these scores may provide an adequate prognostic value for in-hospital major MB. Consequently, we evaluated some well-known bleeding scores to predict in-hospital MB in patients with APE who were treated with thrombolytic therapy.

Materials and Methods: A total of 99 consecutive patients with APE who underwent thrombolytic therapy from June 2011 to August 2015 were included in the retrospective study. For each patient, we estimated the bleeding risk using the Kuijer, Riete, Atria, Has-Bled, and PRECISE-DAPT scores.

Results: In total, 22 MB events occurred in 99 (19%) patients following admission. A receiver operating characteristic curve analysis showed that the PRECISE-DAPT score might have an adequate prognostic value for MB (area under curve [AUC] value, 0.770). Meanwhile, the other abovementioned risk scores had poor predictive values (AUC values, 0.612–0.658) for MB.

Conclusion: Despite being developed and validated to determine MB in patients receiving dual antiplatelet treatment, the PRECISE-DAPT score may be useful in estimating the risk of MB in patients with APE who underwent thrombolytic therapy.

Keywords: PRECISE-DAPT score, acute, pulmonary embolism, thrombolytic, bleeding

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INTRODUCTION

Acute pulmonary embolism (APE) is the major complication of venous thromboembolism (VTE) (1). The clinical outcomes of APE are usually quite variable; hence, risk stratification has been demonstrated as useful in direct medical and interventional therapy. Based on clinical and imaging findings, patients with APE are classified into three risk subgroups: low, intermediate, and high. According to current guidelines, thrombolytic treatment is the proposed therapy in APE patients with intermediate and high risk (2). Previous studies have reported that major bleeding (MB) events may range from 21.7% to as high as 25% in patients with APE based on different thrombolytic agents and regimens (3, 4). However, even though thrombolytic therapy has been associated with decreased mortality rates and the risk of recurrent thromboembolic events in intermediate- and high-risk patients with APE, these potential benefits may be overshadowed by an MB increased risk among these patients (5). Therefore, a simple but valuable risk calculator is needed to determine the MB risk in patients with APE treated with thrombolytic therapy.

Some bleeding risk prediction scores, including the Kuijer and the Riete (Registro informatizado de pacientes con enfermedad tromboembólica), have been developed to determine short-term as well as long-term MB events in patients with VTE under anticoagulant therapy (6, 7). Other bleeding-prediction scores, such as Atria (Anticoagulation and risk factors in atrial fibrillation) and the Has-Bled (Hypertension, age, stroke, Bleeding tendency/predisposition, labile international normalized ratios, elderly age/frailty, drugs such as concomitant aspirin/nonsteroidal anti-inflammatory drugs or alcohol excess) score, are available for patients diagnosed with atrial fibrillation (AF) (8, 9). These scores are recommended for estimating the MB risk in newly diagnosed patients with AF before the initiation of anticoagulation treatment (10).

Recently, the PRECISE-DAPT (Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy) score has been proposed to determine the MB risk in patients treated with coronary stent and are under dual antiplatelet treatment (11). In a recent study, the prognostic value of the abovementioned risk scores, except the PRECISE-DAPT score, has been investigated to predict MB events in patients with VTE during anticoagulant treatment (12). However, patients treated with thrombolytic agents were excluded from this study. Therefore, it is unknown whether these scores may adequately predict in-hospital MB events in patients with APE who underwent thrombolytic therapy. Consequently, we have evaluated the prognostic value of

the Kuijer, Riete, Atria, Has-Bled, and PRECISE-DAPT scores to predict in-hospital MB events in intermediate and high-risk patients with APE treated with thrombolytic therapy.

MATERIALS and METHODS

In total, 266 consecutive patients with APE were retrospectively screened from June 2011 to August 2015. Excluded from the study were patients who had one or more of the following risk factors: the presence of a recent acute coronary syndrome event, acute hepatic failure, low-risk APE, anticoagulant drugs use before admission, and a prior episode of APE. Based on these exclusion criteria, 159 patients were not enrolled in the study. An additional five patients were eliminated due to insufficient image computerized tomographic pulmonary angiography (CTPA) quality, while three more patients were not included due to missing clinical data. Finally, 99 intermediate and high-risk patients with APE who had undergone thrombolytic therapy were found to be eligible for this analysis (Fig. 1). The baseline demographic characteristics, including the signs and symptoms, risk factors, and hemodynamic status parameters, were noted upon emergency admission. All variables used in the risk scores were collected from the hospital electronic database. Our local ethics committee allowed to conduct the current study, which was performed according to the principles of the Declaration of Helsinki (approval number: HNEAHKAEK2019/KK/49).

Following the admission of patients to our emergency department, all blood samples were collected. The blood samples were examined using the Cell-Dyn 3700 auto analyzer (Abbott Lab., Illinois, USA). An electronic database in our hospital was used to obtain all results within laboratory parameters. In the study, 100 mg of alteplase agent was applied to all patients intravenously for 2 hours in the event they had no absolute contraindications to this treatment. After the thrombolytic therapy, the standard anticoagulation treatment was given to all patients.

All echocardiographic examinations were performed using the Vivid 5 system (General Electric, Norway) on study patients. The left ventricular ejection fraction was estimated according to the modified Simpson method. According to the standard APE protocol, the multi-slice spiral, 64-slice CTPA machine (Siemens, Erlangen, Germany) was used to diagnose APE. In all patients, an experienced radiologist confirmed the diagnosis of APE after evaluating all CTPA images. An MB event was accepted according to the definition provided in the Control of Anti-coagulation Subcommittee of the International Society on Thrombosis and Hemostasis (ISTH) guidelines (13). All MB events were evaluated by two cardiologists after examining the patients' medical records. In cases of disagreement, the two cardiologists re-evaluated the MB events and came to a joint agreement. The estimated glomerular filtration rate (eGFR) was determined using the modification of diet in renal disease equation (14).

The Windows Statistical Package for the Social Sciences 21.0 (SPSS Inc., Chicago, Illinois, USA) was used to evaluate the statistical analysis. Parameters with continuous distribution were presented as the mean or the median (25–75 percentiles). The continuous parameters were assessed using an either independent t-test or Mann–Whitney U test. The categorical parameters were assessed using the chi-squared test. The independent predictors

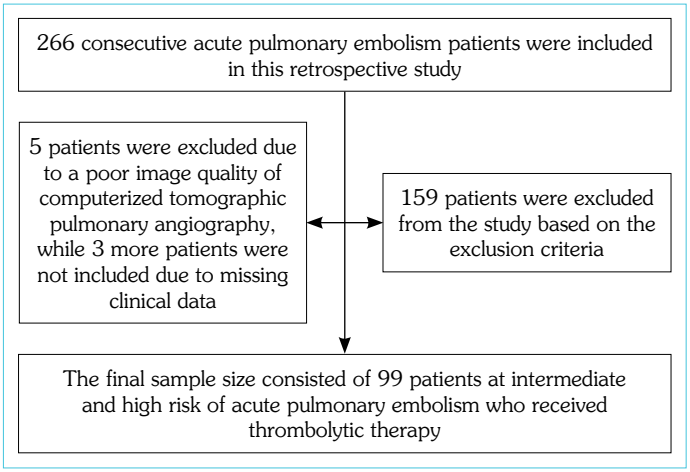

Figure 1. Flow chart of the study population

of MB were found using the multiple binary logistic regression analysis that is a stepwise backward conditional logistic regression analysis. A multiple model included all parameters that reached statistical significance in univariate analysis. The goodness-of-fit test presented an adequate calibration for multiple models (the Hosmer–Lemeshow goodness-of-fit, 4.285; p=0.830). A receiver operating curve (ROC) analysis was performed to determine optimal values of all scores in predicting MB. Pairwise comparison of the ROC curve analysis was performed using the DeLong method. By using the G*Power software, the effect size (Cohen's d) and power value (1–β) of the study were calculated. The effect size and power value were 0.79 and 0.95, respectively. A statistical significance indicated a p-value <0.05.

RESULTS

The mean age of our cohort was 64±16 years, and 44 patients (46.1%) were male. The study cohort was classified into two groups: patients with MB and a control. In total, 22 MB events occurred in 99 (19%) patients during their in-hospital course. Four (18.1%) of the 22 MB events were intracranial, 9 (40.9%) were gastrointestinal, 3 (13.6%) were intramuscular, 2 (9.0%) were retroperitoneal, and 4 (18.1%) were on other locations. Out of those 22, three (13.6%) bleeding events were fatal in patients experiencing an MB complication.

The baseline clinical features, as well as the electrocardiographic, echocardiographic, and laboratory features of all patients, are shown in Table 1. The clinical features were indifferent between the groups (p>0.05 for each). In addition, electrocardiographic and echocardiographic features did not achieve statistical significance between the two groups (p>0.05 for each). In terms of laboratory features, we noted that only the white blood cell (WBC) count (p<0.001), creatinine kinase-myocardial band (p=0.031), and eGFR levels (p=0.042) were statistically different between the two groups.

The mean or median values of bleeding risk scores for each group are demonstrated in Table 2. The median value of the Kuijer (1.6 [1.6–2.9] versus 1.6 [1.3–2.9], p=0.042), Riete (2.5 [2–3.5] versus 2 [1–2.5], p=0.019), and Atria scores (3.5 [3–6] versus 3 [1–4], p=0.045) in patients with MB were significantly higher. Similarly,

Table 1. Baseline demographic characteristics, electrocardiographic, and echocardiographic features of all patients, patients with major bleeding, and control

	All patients (n=99)		Control (n=77)		Major bleeding (n=22)		p
	n	%	n	%	n	%	
Age, years	64±16		62±16		71±13		0.036
Female, gender	55	53.9	42	52.5	13	59.1	0.585
History							
Hypertension	65	63.7	50	30.7	15	44.1	0.625
Diabetes mellitus	35	34.3	26	32.5	9	40.9	0.464
Coronary artery disease	30	29.4	23	28.8	7	31.8	0.781
Current smoking status	56	54.9	46	57.5	10	45.5	0.317
Congestive heart failure	11	10.8	7	8.8	4	18.2	0.209
Chronic obstructive pulmonary disease	25	24.5	19	23.8	6	27.3	0.735
Chronic kidney disease	12	11.8	10	12.5	2	9.1	0.662
Anemia	43	42.2	30	37.5	13	59.1	0.071
Malignancy	6	5.9	4	5	2	9.1	0.472
Alcohol and drug abuse	15	14.7	12	15	3	13.6	0.874
Abnormal liver function	11	10.8	7	8.8	4	18.2	0.209
At admission							
Systolic blood pressure, mm/Hg	116.0±26.0		118.0±27.0		109.0±24.0		0.109
Fever	37.0±0		37.0±0		37.0±0		0.630
Heart rate, beats per minute	116±19		115±18		120±20		0.147
Respiratory rate, beats per minute	21±3		21±3		21±4		0.681
O^2 saturation, %	89±8		89±8		87±9		0.199
Deep vein thrombosis	38	37.3	31	38.8	7	31.8	0.553
Post-surgical immobilization	31	30.4	23	28.8	8	36.4	0.494
Admission laboratory variables							
Admission creatine kinase-MB, ng/mL	22.0±17.0		21.0±17.0		29.0±20.0		0.031
Admission D-dimer, ng/mL	2983±1562		2884±1799		3339±1342		0.813
Admission troponin I, ng/dL	0.40±0.20		0.40±0.20		0.30±0.20		0.810
Creatinine, mg/dL	1.15±0.48		1.11±0.47		1.32±0.51		0.077
Estimated glomerular filtration rate, mL/min	59.0±25.0		62.0±25.0		49.0±21.0		0.042
White blood cell count, cells/µL	12.0±4.4		11.0±3.0		16.0±6.0		<0.001
Hemoglobin, g/dL	13.0±4.0		13.0±2.0		14.0±7.0		0.179
Alanine aminotransferase, U/L	29.0±16.0		29.0±17.0		33.0±16.0		0.520
Electrocardiographic parameters							
Normal sinus rhythm	93	91.2	73	91.3	20	90.9	0.960
RBBB	49	48.0	39	48.8	10	45.5	0.785
S1Q3T3	63	61.8	51	63.8	12	54.5	0.434
Atrial dysrhythmia	11	10.8	7	8.8	4	18.2	0.209
T-wave inversion, (leads V 1-3),	36	35.3	32	40.0	4	18.2	0.059
Echocardiographic parameters							
LVEF, %	58.0±7.0		58.0±7.0		60.0±6.0		0.354
RV dilatation	99	100	77	100	22	100	1.000
RV S' velocity, cm/s	9.0±2.0		9.0±2.0		9.0±2.0		0.159
RV TAPSE	12.0±2.0		12.0±2.0		12.0±1.0		0.753
PASP, mmHg	55.0±12.0		54.0±11.0		58.0±18.0		0.431
Tricuspid regurgitation							
None	3	2.9	2	2.5	1	4.5	
Mild	27	26.5	22	27.5	5	22.7	
Moderate	39	38.2	32	40.0	7	31.8	0.439
Moderate-severe	32	31.4	24	30.0	8	36.4	
Severe	1	1.0	0	0	1	4.5	
Simple PESI score	2.0 (1.0–3.0)		2.0 (1.0–3.0)		2.0 (2.0–3.0)		0.050
Major bleeding							
Intracranial	4	18.1	0	0	4	18.1	
Gastrointestinal	9	40.9	0	0	9	40.9	
Intra-muscular	3	13.6	0	0	3	13.6	
Retroperitoneal	2	9.0	0	0	2	9.0	
Other locations	4	18.1	0	0	4	18.1	

Continuous variables are presented as mean±SD. Nominal variables presented as frequency (%). n: number; RBBB: Right bundle branch block; LVEF: Left ventricular ejection fraction; RV: Right ventricle; TAPSE: Tricuspid annular plane systolic excursion; PASP: Pulmonary artery systolic pressure; PESI: Pulmonary embolism severity index

Table 2. Mean and median value of all bleeding risk scores of all patients

	All patients (n=99)	Control (n=77)	Major bleeding (n=22)	p
PRECISE-DAPT score	27.0±11.0	25.0±11.0	36.0±9.0	<0.001
Atria score	3.0 (1.0–4.0)	3.0 (1.0–4.0)	3.5 (1.0–6.0)	0.045
Has-Bled score	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (2.0–2.0)	0.093
Kuijer score	2.25 (1.0–3.0)	2.0 (1.0–2.5)	2.5 (2.0–3.5)	0.042
Riete score	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (2.0–2.0)	0.019

All data are presented as mean±standard deviation or median. Riete: Registro informatizado de pacientes con enfermedad tromboembólica; Atria: Anticoagulation and risk factors in atrial fibrillation; Has-Bled: Hypertension, age, stroke, Bleeding tendency/predisposition, labile international normalized ratios, elderly age/frailty, drugs such as concomitant aspirin/nonsteroidal anti-inflammatory drugs or alcohol excess; PRECISE-DAPT: Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy

the mean value of simple pulmonary embolism severity index (2±2 versus 2±1, p=0.05) and PRECISE-DAPT scores (36±9 versus 25±11, p<0.001) were also significantly elevated in patients with MB. Meanwhile, the median value of the Has-Bled score was indifferent between the groups (2 [1–2] versus 2 [2–2], p=0.093).

In Figure 2, the ROC curves of the Kuijer, Riete, Atria, Has-Bled, and PRECISE-DAPT scores for MB are shown. The area under curve (AUC) value of the PRECISE-DAPT score was the highest with 0.770 (0.671–0.869; 95% CI [confidence interval]), followed by the AUC of the Riete score with 0.657 (0.536–0.779; 95% CI), followed by Kuijer with the AUC of 0.638 (0.523–0.752; 95% CI), Atria with the AUC of 0.638 (0.509–0.767; 95% CI), and Has-Bled with the AUC of 0.612 (0.493–0.731; 95% CI). All differences in AUC values were significant along with all p-values of <0.05. The optimal value of the PRECISE-DAPT score was >23 for the prediction of MB (sensitivity, 95.4%; specificity, 51.2%). The predictive value of the PRECISE-DAPT score regarding occurrence of MB was superior compared to the Kuijer, Riete, Atria, and Has-Bled scores in a pairwise comparison of the ROC curve analysis. Figure 3 shows the ROC curve analyses of PRECISE-DAPT, age, WBC count, and hemoglobin to predict MB. We also observed that the prognostic power of the PRECISE-DAPT score was superior to age, the WBC count, and hemoglobin in predicting MB.

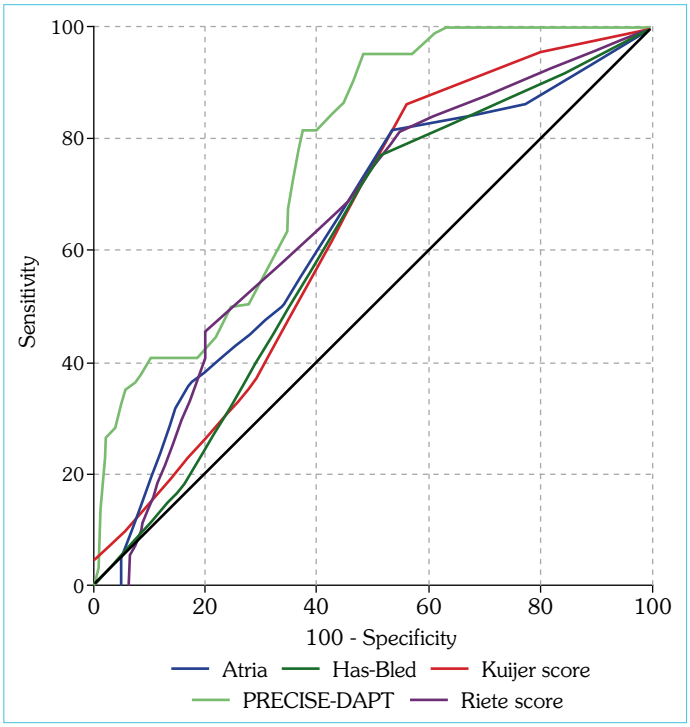

Figure 2. The receiver operating characteristic (ROC) curves of the bleeding risk scores for major bleeding. A pairwise comparison of ROC curves showed that the predictive value of the PRECISE-DAPT score with regards to major bleeding was superior compared to other bleeding risk scores

ROC: Receiver operating characteristic curve

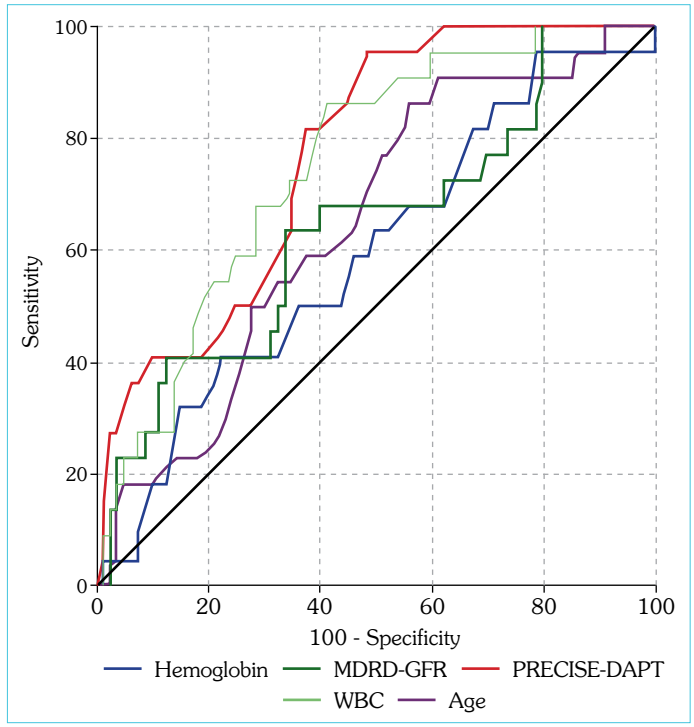

Figure 3. The receiver operating characteristic (ROC) curves of the PRECISE-DAPT score, white blood cell count, age and hemoglobin level for major bleeding. A pairwise comparison of ROC curves showed that the predictive value of the PRECISE-DAPT score with regards to major bleeding was superior compared to its components

ROC: Receiver operating characteristic curve

Table 3. Univariate analysis and multiple binary logistic regression analysis for major bleeding*

Univariate analysis	p	OR (95% CI)	Multiple binary logistic regression analysis	p	OR (95% CI)
Age	0.031	1.041 (1.004–1.079)	–	–	–
PRECISE-DAPT score	<0.001	1.101 (1.046–1.179)	PRECISE-DAPT score	0.001	1.105 (1.042–1.172)
eGFR	0.031	0.974 (0.951–0.998)	–	–	–
WBC count	0.009	1.228 (1.052–1.433)	WBC count	0.013	1.250 (1.048–1.490)

*All clinically relevant parameters were included in the model. CI: Confidence interval; eGFR: Estimated glomerular filtration rate; PRECISE-DAPT: Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Anti-Platelet Therapy; OR: Odds ratio; PESI: Pulmonary Embolism Severity Index; WBC: White blood cell

Table 3 presents the independent prognosticator of MB. Age, the PRECISE-DAPT score, eGFR, and WBC count were found to be prognosticators of MB by univariate analysis. In a multiple binary logistic regression analysis, only the WBC count (OR [odds ratio], 1.250; 95% CI, 1.048–1.490; p=0.013) and the PRECISE-DAPT score (OR, 1.105; 95% CI, 1.042–1.172; p=0.001) were independent prognosticators of MB.

DISCUSSION

In the present cohort, our head-to-head comparison of some well-known and extensively validated bleeding risk scores in patients with APE showed that only the PRECISE-DAPT score provided an adequate prognostic value (AUC, 0.770) for the prediction of MB.

The clinical manifestations of APE are usually quite variable and may range from mild dyspnea to shock (2). In accordance with current guidelines, APE is classified as either low, intermediate, or high risk to make decisions about necessary therapy. In addition, risk stratification is also performed to determine risk of complications. Patients with intermediate and high MB risk are usually suitable for the treatment with thrombolytic therapy (15). Currently, three thrombolytic agents (streptokinase, urokinase, and alteplase) are available for this indication, and the MB risk may depend on the type and amount of thrombolytic agent used (5). Patients who were only treated with alteplase were included in our study. Previous studies demonstrated that thrombolytic therapy is associated with relieving symptoms, preventing recurrent APE events, and reduced mortality rates. However, these benefits may be counterbalanced with the MB risk (16). Unfortunately, there is no guideline-based risk tool to determine the MB risk in patients with APE undergoing thrombolysis.

Thus far, some well-known bleeding-prediction scores have been investigated in patients with APE during anticoagulant treatment. In a previous prospective cohort study, the Kuijer and Riete scores were examined to estimate the MB risk in patients with acute VTE under anticoagulation treatment (17). That study concluded that the predictive value of these scores was fair, with the AUC values ranging from 0.49 to 0.60. In addition, Riva et al. studied Has-Bled scores in 681 patients with VTE and reported that the Has-Bled score had a modest predictive value for MB during anticoagulant treatment (18). Furthermore, a recent observational cohort study examined the prognostic value of the Kuijer, Has-Bled, Riete, and Atria scores in 448 consecutive patients with APE who were treated with heparins followed by vitamin K antagonists, and they found that the predictive values of all the scores for MB were poor to moderate (AUC, 0.57–0.64) (12).

Until now, to the best of our knowledge, there has been no studies to evaluate the relation between some bleeding risk scores and MB events in patients with APE who are treated with thrombolytic therapy because these patients have been excluded from the studies. We therefore sought to investigate the predictive power of several bleeding risk scores including Kuijer, Riete, Atria, Has-Bled, and PRECISE-DAPT in patients with APE who are treated with thrombolytic treatment. Of these bleeding risk scores, the PRECISE-DAPT score had the highest AUC (0.770) value. So, what might be an underlying mechanism for the higher prognostic value of the PRECISE-DAPT score compared to the other bleeding risk scores? We speculate that compared to parameters included in the other bleeding risk scores, the WBC count, which is an inflammatory marker and component of the PRECISE-DAPT score, may be an important contributor because it was an independent predictor of MB in multiple analyses in the current study. Also, the association of an elevated WBC count and MB has been described in the myocardial infarction patients with ST-segment elevation who underwent thrombolytic treatment (19). The findings from previous studies have revealed that there is an independent association between the WBC count and MB in patients with acute coronary syndrome (20). Moreover, the elevated levels of the WBC count have been reported as an independent prognosticator of elevated perioperative bleeding in patients undergoing cardiac surgery (21). However, a ROC curve comparison revealed that the prognostic value of the PRECISE-DAPT score was superior for MB compared to its components, including the WBC count.

The PRECISE-DAPT score has recently added a simple 5-item risk score that can be used to estimate the MB risk in patients under dual antiplatelet therapy following percutaneous coronary intervention. Despite being developed and validated for predicting MB, the PRECISE-DAPT score may also be beneficial for predicting MB in patients with APE, as shown in the current study. The application of the PRECISE-DAPT score in daily clinic practice should be done carefully in patients with APE. Even though a PRECISE-DAPT score ≥23 was demonstrated to have a high sensitivity (95.4%) for the prediction of MB in the study, the specificity of this cut-off value was only 51.2%. So how can we use the

PRECISE-DAPT score in daily practice in patients with intermediate- and high-risk APE? First, we stress that withholding thrombolytic therapy is unreasonable based on the predictive value of the bleeding risk score since thrombolytic treatment has been related to decreased mortality and risk of recurrent thromboembolic events among patients. Nevertheless, we suggest that clinicians take appropriate preventive bleeding measures, such as control of high blood pressure or withholding any antiplatelet therapy in patients with a higher PRECISE-DAPT score. In addition, some strategies should be considered, such as either a weight-adjusted dose regimen, half-dose regimen, or catheter directed therapy for patients considered to be at a high risk for MB based on a higher PRECISE-DAPT score.

Study Limitations

Our study has the following limitations. It has a retrospective design and consists of a relatively small sample size. However, all consecutive patients were enrolled in the study. In addition, the statistical power analysis showed an adequate power for the study. Even though multiple binary logistic regression analysis was performed in the study, there was the possibility of the presence of residual confounding from unmeasured variables that might influence the final result of the study. Moreover, since the definition of MB was only made as proposed by the ISTH criteria, other definitions of bleeding were not used for MB. In addition, a well-known inflammatory marker, C-reactive protein, was not assessed in the current cohort because of missing clinical data. Due to the design of the study, prospective studies with large sample sizes are required to understand the accurate role of the PRECISE-DAPT score for MB in patients with APE who were treated with thrombolytic therapy.

CONCLUSION

This is the first study, to the best of our knowledge, that compared the well-known and extensively validated bleeding scores in patients with APE who underwent thrombolytic treatment. Among these bleeding scores, only the PRECISE-DAPT score had an adequate prognostic power for MB among these patients. Therefore, despite being developed and validated to ascertain the MB risk in patients under dual antiplatelet treatment, the PRECISE-DAPT score may be useful in a risk scoring system to assess MB in patients with APE who underwent thrombolytic therapy.

Ethics Committee Approval: Haydarpaşa Numune Training and Research Hospital, Clinical Research Ethics Committee allowed to conduct the current study, which was performed according to the principles of the Declaration of Helsinki (Date: 20.05.2019; Approval number: HNEAHKAEK2019/KK/49).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – TC, VOT; Design – TC, BS, VOT; Supervision – SA; Fundings – TC, VOT; Materials – BS, VOT; Data Collection and/or Processing – TC, BS; Analysis and/or Interpretation – TC, VOT; Literature Search – BŞ, VOT; Writing – VOT, TÇ; Critical Reviews – SA.

Conflict of Interest: The authors have no conflict of interest to declare.

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