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D-dimer levels enhance the discriminatory capacity of bleeding risk scores for predicting in-hospital bleeding events in acute pulmonary embolism☆

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ABSTRACT

Introduction: Bleeding is a major complication of anticoagulation in acute pulmonary embolism (APE) while estimating individual bleeding risk remains challenging. Elevated D-dimer levels (DD) have been shown to predict bleeding events.

Objectives: (1) direct comparison of the capacity of bleeding risk prediction scores (VTE-BLEED, RIETE, HAS-BLED, HEMORR$_2$HAGES) to prognosticate in-hospital bleeding events in the acute phase of APE in a real-life population of APE patients;(2) augmentation of the discriminative capacity of fore mentioned scores with DD.

Materials: Post-hoc analysis of a prospective observational study. DD levels were measured using the VIDAS D-dimer Exclusion test. Receiver operating characteristic curves, areas under the curve (AUC) for bleeding prediction were calculated for scores and DD. Bleeding scores + DD were compared using an established index quantifying the reclassification of patients (net reclassification index, NRI).

Results: 310 APE patients were included. 35(11.3%) bleeding events occurred (hematomas, GI, urinary tract, retroperitoneal, uterine, CNS, respiratory tract): 17 major (MB) and 18 clinically-relevant non-major bleedings (CRNMB), none were fatal. All scores had satisfactory AUCs (0.754–0.767), except HAS-BLED (AUC = 0.512; 0.455–0.569). DD were higher in patients with bleeding events (29,911 ng/ml vs. 4805 ng/ml, p = .031), AUC 0.621(0.520–0.721), p = .02. DD = 5750 ng/ml was characterized by OR = 2.3(95%CI 1.05–5.0) for all bleeding events. Adding DD improved the discriminatory capacity of tested scores in the non-high risk of bleeding category, NRI 0.07–03.

Conclusions: Of the tested scores RIETE, HEMORR$_2$HAGES, VTE-BLEED performed best at identifying APE patients at risk of in-hospital bleeding complications. DD levels may predict in-hospital bleeding events and may improve identifying patients classified as non-high risk who experience bleeding complications.

1. Introduction

A diagnosis of venous thromboembolism (VTE) requires treatment with anticoagulants for at least three months, which in some groups of patients should be extended, keeping in mind that bleeding remains a common, possibly fatal complication of treatment [1,2]. Currently, most reports classify bleeding according to the definition proposed by the International Society on Thrombosis and Haemostasis (ISTH) into major bleeding (MB) and clinically relevant non-major bleeding (CRNMB). The overall prevalence of this complication in acute pulmonary embolism (APE) cohorts is approximately 10/100 patient-years [3]. In the elderly population, in which the risk of APE is increased due to advanced age, this finding is even more pronounced, with the risk of major bleeding including intracerebral bleeding doubling in patients aged above 80 years [4–7]. As the risk of hemorrhagic complications is highest in the early days of treatment, in this study we focus on the occurrence of in-hospital events. The ability to properly evaluate bleeding risk is mandatory and should guide anticoagulation, as

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patients classified at a higher risk of bleeding can benefit from closer anticoagulation monitoring. However, prognosticating the risk of bleeding events remains challenging. Several bleeding risk prediction scores have been proposed, including the VTE-BLEED, RIETE, HAS-BLED, and HEMORR$_2$HAGES scores [8–17]. It should be underlined that these reports have several limitations: most are retrospective, few focus on real-life cohorts, included are patients in the stable (not acute) phase of anticoagulation. This discrepancy is of importance, as the discriminatory capacity of bleeding risk scores varies between studies used to derive them and subsequent real-life studies [8–10].

Serum D-dimer (DD) levels are routinely measured in patients with suspected APE [1]. In this population, elevated DD levels have been demonstrated to correspond with right ventricular dysfunction and the occurrence of serious adverse events [18,19]. It has been shown in a sub-population of cancer-free APE patients included in the REITE registry that markedly elevated DD levels predict the occurrence of fatal bleeding [20,21]. Therefore, we hypothesize that DD levels may be useful in the identification of patients at risk of MB and CRNMB events.

The purpose of this study was: (1) to compare the VTE-BLEED, RIETE, HAS-BLED, and HEMORR$_2$HAGES risk scores in their capacity to estimate the probability of the occurrence of major and clinically relevant non-major in-hospital bleeding during the initial phase of therapy in a real-world cohort of unselected patients with APE; (2) to establish whether DD levels measured at admission may be incorporated into predicting in-hospital bleeding complications in APE patients; (3) to augment the fore mentioned risk scores with DD levels measured at admission and to establish whether this modification can augment the discriminatory capacity of bleeding risk prediction scores.

2. Methods

This is a *post-hoc* analysis of a prospective observational cohort of consecutive patients hospitalized with APE at a single reference center between January 2013 and June 2017. Patients were taken from the original "PE-aWARE" registry, which encompasses all APE patients treated at our center (NCT03916302). The inclusion criteria were as follows: symptoms suggestive of APE lasting no longer than 14 days, an objectively confirmed diagnosis of acute pulmonary embolism, date of hospitalization within the mentioned timeframe, measured D-dimer levels. Patients who did not give informed consent, or with symptoms lasting longer than 14 days before admission, or with sub-segmental level thrombi were excluded. Treatment was left at the discretion of the treating physician. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's ethics committee.

APE was confirmed by contrast-enhanced MSCT when thromboemboli were visualized at least at the level of segmental pulmonary arteries and in one case of inconclusive MSCT findings with a positive ultrasonographic lower-limb venous compression test. MSCT angiography was performed using 64-row Toshiba Aquilion (Toshiba Medical Systems, Otawara, Japan) or 16-row GE LightSpeed Pro systems (General Electric Medical Systems, Waukesha, Wisconsin, United States). The results of MSCT studies were adjudicated by two radiology specialists. The ultrasonographic lower-limb compression test was performed by a trained radiologist with the Philips XD11XE system (Philips Medical Systems, Best, the Netherlands) using a linear transducer (L12 − 3) according to the standard protocol.

Plasma DD concentrations were quantitatively measured on the day of admission to the Emergency Department as part of a standard diagnostic workup using an automated enzyme-linked fluorescent assay with a reference range of values up to 500 ng/ml (VIDAS D-dimer Exclusion, bioMerieux, France).

Information on the occurrence of bleeding was taken from patient charts and verified by two independent researchers. Included were bleeding events which fulfilled the classification proposed by the ISTH as (1) major bleeding (MB) defined as fatal bleeding, and/or symptomatic bleeding in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular, bleeding with a reduction of hemoglobin ≥ 2 g/dl, and/or bleeding leading to a transfusion of ≥ 2 units of packed red blood cells or whole blood or (2) clinically relevant non-major bleeding (CRNMB) defined as any sign or symptom of hemorrhage that does not meet the criteria for a major bleed but prompts a clinical response, understood as one of the following: a hospital admission for bleeding or an increased level of care, a face-to-face evaluation, or requires medical attention by a healthcare professional [22,23]. Any drop in hemoglobin levels which could be attributed to dilution (i.e. in a patient without clinical signs of bleeding) was not included as a bleeding event.

Bleeding risk prediction scores were calculated retrospectively by researchers blinded to the data on the occurrence of bleeding using data obtained from patient charts. Exact definitions used in original publications and/or supplementary materials (where applicable) were applied [11,13,14,17]. Similarly to prior publications and due to the real-life cohort nature of this study, some variables were not available, namely data on the presence of the CYP2C9*2 or CYP2C9*3 mutation or on liable INR values (listed in the footnote below Fig. 1). Basing on the total number of obtained points in each score, patients were classified as low-, intermediate-, or high- risk of bleeding. The variables included in each of the bleeding risk prediction scores and the corresponding point values, as well as, the cut-off values for bleeding risk categories are presented in Fig. 1.

Missing values were considered normal (for CYP2C9*2 or CYP2C9*3 mutations for the HEMORR$_2$HAGES score and liable INR for HAS-BLED), this approach has been previously used in the clinical application of prognostic models [10].

The study endpoint was the occurrence of a first in-hospital bleeding event classified as MB or CRNMB.

Baseline characteristics of patients are presented as parameter or median followed by interquartile range. The Shapiro-Wilk test was used to identify continuous variables with a skewed distribution which were then compared using the Mann-Whitney *U* test or Chi-square test. All tests were two-sided. For all performed tests *P*-values of < 0.05 were considered significant. Receiver operating characteristic (ROC) analysis was used to determine the area under the curve (AUC) and the corresponding 95% confidence intervals (CIs) for each bleeding risk score in relation to the occurrence of the first bleeding event. The DeLong test was used for pair-wise comparisons of the obtained AUCs. Next, the prognostic relevance of DD levels was assessed using univariable analysis and a threshold for DD levels based on ROC curve analysis was selected. To validate whether DD levels could improve the prognostic capacity of bleeding risk scores the net reclassification improvement for each of the bleeding risk prediction scores and DD above the threshold was calculated using the method described by Pencina et al. [24]. For non-binary bleeding risk scores (e.g. HEMORR$_2$HAGES and RIETE) a threshold based on the ROC curve and using Youden's index was selected to divide the study group into non-high risk and high-risk of bleeding subpopulations. All analyses were performed using the STATISTICA 13 data analysis software system (Dell Software, USA) or the MedCalc data analysis software system (MedCalc Software, Belgium).

3. Results

The final analysis comprised 310 consecutive patients (162 female (52.2%), median age 65 years (25th–75th percentile, 49–81) with objectively confirmed APE. The flow of patients is presented in Fig. 2. According to the ESC guidelines, at admission 85 patients were classified as low-risk of early mortality, 216 patients as intermediate-risk (intermediate-low 84 pts., intermediate-high 132 pts), and 9 patients as high-risk. The mortality rate was 2.6%. The median length of hospital stay was 6.5 days (5–9 days). Full patient characteristics are presented in Table 1. Methods of treatment are summarized in Table 2. Overall,

Score (point value)	HAS-BLED		HEMORR$_2$HAGES		RIETE		VTE-BLEED	
Variables	hypertension	1	hepatic or renal disease	1	recent bleeding	2	active cancer	2
	abnormal liver function	1	ethanol abuse	1	abnormal renal function	1.5	male pt with uncontrolled hypertension	1
	abnormal kidney function	1	malignancy	1	anemia	1.5	anemia	1.5
	Stroke	1	age ≥ 75 yrs	1	age > 75 yrs	1	history of bleeding	1.5
	bleeding history or predisposition	1	reduced platelet count or function	1	active malignancy	1	renal dysfunction	1.5
	labile INR	1	prior bleeding	2	clinically overt PE	1	age ≥ 60 yrs	1.5
	age ≥ 65 yrs	1	hypertension	1				
	drug abuse	1	anemia	1				
	alcohol abuse	1	genetic factors	1				
			excessive fall risk	1				
			prior stroke	1				
Cut-off values (points)								
Low risk	0-2		0		0		0-2	
Intermediate risk	-		2-3		1-4		-	
High risk	>3		>3		>4		>2	

Fig. 1. Bleeding risk prediction scores. Abbreviations: pt-patient; yrs-years.
For HEMORR2HAGES, no information on "genetic factors" defined as a mutation in CYP2C9*2 or CYP2C9*3 was provided. Creatinine clearance was estimated from the Cockroft-Gault formula where body mass was available or from the MDRD formula in other cases. Patients with history of a transient ischemic attack were also included in the "stroke" category. "Excessive fall risk"- Patient charts were review for information on the actual event of falling during hospitalization or on proneness to falling before hospitalization or on neurological conditions predisposing to falling (dementia, Parkinson's disease). For HAS-BLED no patient received points for "liable INR", creatinine clearance was calculated as above. For RIETE all patients received one point for "PE diagnosis", "anemia" was defined as hemoglobin levels below 13 g% for men and below 12 g% for women. For VTE-BLEED "uncontrolled hypertension" was defined as systolic blood pressure above 140 mmHg. "Anemia" was scored identically to RIETE.

patients were administered at least one of the following: thrombolysis (alteplase), unfractionated heparin, low molecular weight heparin, fondaparinux, rivaroxaban, dabigatran, acenocoumarol, warfarin.

Bleeding score values for each of the bleeding prediction scores for both subgroups (hemorrhagic event and no hemorrhagic event) are presented in Table 3.

A full summary of bleeding events including bleeding sites is presented in Table 4. There were 35 bleeding events in 35 patients (11.3% of pts), 17 MBs (5.5%) and 18 CRNMBs (5.8%). Only one observed bleeding event (MB) occurred in a thrombolysed patient, who died with no follow-up autopsy. No bleeding event was classified as fatal. The median time to the first bleeding event was 3.5 days (25th–75th percentile 1–8.3 days).

The calculated AUCs for each of the bleeding risk prediction scores for MB and CRNMB along with significance levels are presented in Fig. 3. All scores apart from HAS-BLED were characterized by a satisfactory c-statistic for the prediction of the in-hospital occurrence of MB and CRNMB.

Based on ROC curve analysis, a cut-off point for the dichotomized division of patients into non-high risk and high-risk subgroups for HEMORR$_2$HAGES and RIETE bleeding risk scores was selected (above 3 points for HEMORR$_2$HAGES: sensitivity 0.67, specificity 0.72, and above 4 points for RIETE: sensitivity 0.60, specificity 0.80).

Serum DD levels were higher in patients who suffered an MB or a CRNMB event (29,911 ng/ml vs. 4805 ng/ml, $p = .031$). The AUC for DD levels in predicting any bleeding event was 0.621 (95% CI 0.520–0.721), $p = .018$ (Fig. 4). The DD level of 5750 ng/ml was calculated as the optimal cut-off level, characterized by equal sensitivity and specificity in regard to the occurrence of all analyzed bleeding events (accuracy 60%), OR = 2.3 (95% CI 1.05–5.00), $p = .035$.

DD levels > 5750 ng/ml in combination with low-risk of bleeding defined according to the fore mentioned score thresholds displayed an improved capacity for the predication of bleeding events, as shown in Table 5. The RIETE, HEMORR$_2$HAGES, and HAS-BLED scores demonstrated the highest net reclassification improvement, whereas the VTE-BLEED score was only modestly improved.

4. Discussion

In this post-hoc analysis of a prospective observational study, we demonstrate in a real-life cohort of APE patients that the RIETE, HEMORR$_2$HAGES, and VTE-BLEED bleeding risk prediction scores sufficiently identify patients in the early phase of treatment at risk of in-hospital bleeding complications, with AUCs ranging from 0.767 to 0.754 and no superiority over one another. Importantly, we found the HAS-BLED score to have a very limited prognostic value for the prediction of in-hospital hemorrhagic events. Moreover, in this study DD levels measured at admission were useful in predicting major and non-major clinically relevant bleeding events, which adds to their already established diagnostic and prognostic potential in APE [1,18–21].

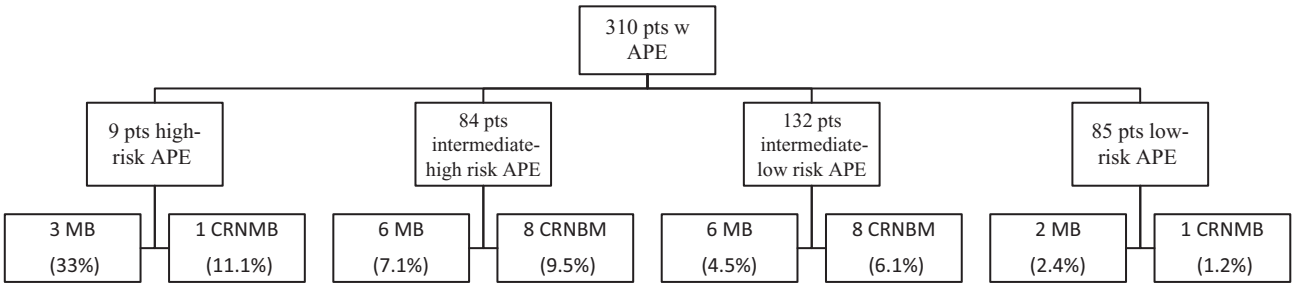

Fig. 2. Flow of patients, presented are risk of early mortality according to ESC guidelines and number of bleeding events. Abbreviations: CRNMB- clinically relevant non-major bleeding; MB- major bleeding; pts-patients.

Table 1
Patient characteristics. Parameters are presented as number (percentage) or median followed by interquartile range. Parameters are compared using Mann-Whitney *U* test or Chi square test, where appropriate. Abbreviations: ALT- alanine transaminase; AST- aspartate transaminase; CRNMB- clinically relevant non-major bleeding; DD- d-Dimer level; DAPT- double anti-platelet therapy; Hgb- hemoglobin level (g/dl); MB- major bleeding; max crea- maximal plasma creatinine concentration; pts-patients; No- number; NS- not significant; SBP- systolic blood pressure.

Parameter	Non-hemorrhagic pts (275 pts)	MB (17 pts)	CRNMB (18 pts)	P (non-hemorrhagic vs. hemorrhagic pts)
Age (yr, median)	64 (48.5–80)	78 (62–85)	70 (57.5–84)	0.02
Female (%)	143 (52%)	8 (47.1%)	11 (61.1%)	NS
Hospital stay length (days)	6 (5–8)	15 (11 − 20)	7 (6–11.75)	0.001
SBP (mmHg)	130 (120–140)	130 (110–145)	130 (120–150)	NS
Weight (kg)	80 (68–93.9)	80 (68–95)	72 (64.1–82.5)	NS
DD (ng/ml)	4805 (2083–11,294)	5901 (4560–19,542)	6343 (3907–12,462)	0.03
Hgb min (g/dl)	12.06 (11.3–13.8)	9.4 (7.5–10.2)	11.40 (9.8–12.6)	< 0.001
DAPT	2 (0.7%)	1 (5.9%)	0 (0%)	NS
Arterial hypertension (%)	92 (33.8%)	7 (41.2%)	9 (50%)	NS
Previous stroke (%)	23 (8.4%)	2 (11.8%)	0 (0%)	NS
Liver disease (no of pts)	3 (1.1%)	0 (0%)	1 (5.6%)	NS
History of bleeding (%)	14 (5.1%)	4 (23.5%)	7 (38.9%)	0.001
Neoplasm (no of pts)	45 (16.4%)	8 (47.1%)	3 (16.7%)	0.03
AST (U/L)	22 (18–37)	26 (19.3–34.3)	21 (19–26)	NS
ALT (U/L)	23.5 (15–43.3)	20 (13–29.5)	20 (13 − 22)	0.03
Max plasma crea (mg/dl)	1 (0.8–1.2)	1.2 (0.9–1.5)	1.0 (0.8–1.5)	0.04
Mortality risk:				
Low risk	82 (29.8%)	2 (11.8%)	1 (5.6%)	0.008
Intermediate risk	188 (68.4%)	12 (70.6%)	16 (88.8%)	0.001
High risk	5 (1.8%)	3 (17.6%)	1 (5.6%)	0.001

Finally, in this exploratory analysis, we demonstrate that augmenting bleeding risk prediction scores with DD levels modestly improves their discriminatory capacity, as shown by NRIs of 0.07–0.30, except for VTE-BLEED, which was improved only to a small extent (NRI 0.07, $p < .05$). However, it is worth underlining that this score was initially designed for bleeding risk assessment in VTE patients on stable anticoagulation [11]. Similar observations regarding both increased frequencies of major bleeding in patients with elevated DD levels and of an incremental benefit from adding DD to the HAS-BLED score in patients anticoagulated for atrial fibrillation have been reported before in a large population originally included in the ARISTOTLE trial [25], as well as in patients from the RIETE registry [19,20].

The satisfactory AUCs for bleeding prediction scores which we obtained are more optimistic than those published by others [10,11,15]. We attribute this to several factors. Firstly, the definitions for variables included in the risk scores are not clearly defined (e.g. anemia in the RIETE score). Due to this limitation, individual studies have used divergent cut-offs which in turn may have influenced the reproducibility of results. In our study, we opted for more lenient criteria. Second, the occurrence of bleeding events in our study population was quite high. This may be explained by the high prevalence of factors predisposing to bleeding such as neoplasm (18% of pts) and chronic kidney disease (57.1%). It is noteworthy that the latter subgroup is usually omitted from studies, especially from controlled randomized trials. The rate of non-major clinically relevant events in the studied population was high (5.8% pts). It should be underlined that most clinical trials, as well as, registries focus on major bleeding only [8,11,14,26,27]. Third, in this study, we chose to include patients with a high probability of neoplasm, and not only those with a definite diagnosis, as we believe this better reflects clinical judgment when introducing anticoagulation treatment. This factor may have contributed to the low AUC of the HAS-BLED score, which does not include neoplasm as a variable and may be partially responsible for its underperformance, as has been stated by others [15,16]. Lastly, patients on all types of treatment were analyzed, including those who were thrombolysed and those on direct oral anticoagulants.

In our cohort, patients with higher DD levels were more likely to suffer from any bleeding complication. A similar finding was reported for non-cancer patients included in the RIETE registry and ARISTOTLE trial, whereas in acute coronary syndromes higher DD levels prognosticated mortality [21,25,28–30]. Moreover, elevated DD levels have been shown to correspond with overall mortality in APE patients, with bleeding remaining one of the main causes of mortality in elderly APE patients [7,18–20]. We speculate that this association may be explained by a higher clot burden resulting in more severe alterations of the clotting system, as well as patient-dependent factors contributing to an elevated risk of bleeding, such as advanced age and the presence of deep vein thrombosis, which have been demonstrated to be related to higher DD concentrations and to influence mortality. Specifically, we show that bleeding risk scores in combination with DD levels above the

Table 2
Summary of treatment types. Parameters are presented as number of patients (percentage). Abbreviations: CRNMB- clinically relevant non-major bleeding; LMWH-low molecular weight heparin; MB- major bleeding; No- number; pts-patients; UHF-unfractionated heparin.

Treatment, percentage of overall pts (310 pts)	Non-hemorrhagic pts (275 pts)	Treatment at occurrence of MB (17 pts)	Treatment at occurrence of CRNMB (18 pts)
Thrombolysis (alteplase), 5 (1.6%)	4 (1.4%)	1 (5.9%)	0 (0%)
UHF, 33 (10.6%)	29 (10.5%)	2 (11.8%)	2 (11.1%)
LMWH, 261 (84.1%)	239 (87%)	11 (64.7%)	11 (61.1%)
Fondaparinux, 3 (0.9%)	3 (1.1%)	0 (0%)	0 (0%)
Rivaroxaban, 174 (56.1%)	172 (62.5%)	0 (0%)	2 (11.1%)
Dabigatran, 14 (4.5%)	13 (4.7%)	0 (0%)	1 (5.6%)
Acenocoumarol or warfarin alone, 5 (1.6%)	5 (1.8%)	0 (0%)	0 (0%)
Combination therapy, LMWH + acenocoumarol/warfarin, 30 (9.7%)	15 (5.4%)	LMWH + acenocumarol/warfarin 3 (17.6%)	LMWH + warfarin/acenocumarol 2 (11.1%)

Table 3
Bleeding risk score values. Parameters are presented as median or number of patients and percentage. Abbreviations: CRNMB- clinically relevant non-major bleeding; MB- major bleeding; pt-points.

Bleeding prediction score Bleeding risk	All pts (310)	Non-hemorrhagic pts (275)	MB (17)	CRNMB (18)
VTE-bleed	3	2.5	5.5	3
Low risk (< 2 pt)	131 (42.3%)	126 (45.8%)	1 (5.9%)	4 (22.2%)
High risk (≥ 2 pt)	179 (57.7%)	149 (54.2%)	16 (94.1%)	14 (77.8%)
RIETE	2.5	2.5	5.5	3.5
Low risk (0 pt)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Intermediate risk (1–4 pt)	256 (82.6%)	242 (88.0%)	6 (35.3%)	8 (44.4%)
High risk (> 4 pt)	54 (17.4%)	33 (12.0%)	11 (64.7%)	10 (55.6%)
$HEMORR_2HAGES$	1.5	1	3	3
Low risk (0–1 pt)	155 (50.0%)	150 (54.5%)	2 (11.8%)	3 (16.7%)
Intermediate risk (2–3 pt)	99 (31.9%)	82 (29.8%)	7 (41.1%)	10 (55.6%)
High risk (> 3 pt)	56 (18.1%)	43 (15.7%)	8 (47.1%)	5 (27.7%)
HAS-BLED	1	1	1	1
Low risk (< 3 pt)	286 (99.3%)	254 (92.4%)	17 (100%)	15 (88.3%)
High risk (≥ 3 pt)	24 (7.7%)	21 (7.6%)	0 (0%)	3 (16.7%)

Table 4
Summary of bleeding events. Parameters are presented as number of patients and percentage. Abbreviations: CRNMB- clinically relevant non-major bleeding; CNS- central nervous system; MB- major bleeding; pts- patients.

Site of hemorrhagic complication	MB (17 pts)	CRNMB (18 pts)
Hematoma (subcutaneous tissue of limbs)	5 (29.4%)	2 (11.1%)
Gastrointestinal tract	3 (17.6%)	2 (11.1%)
Urinary tract	3 (17.6%)	6 (33.3%)
Retroperitoneal	2 (11.8%)	0 (0%)
Uterine (post-menopausal)	2 (11.8%)	4 (22.2%)
CNS	1 (5.9%)	0 (0%)
Respiratory tract	1 (5.9%)	Intense hemoptysis 3 (16.7%); epistaxis 1 (5.6%)

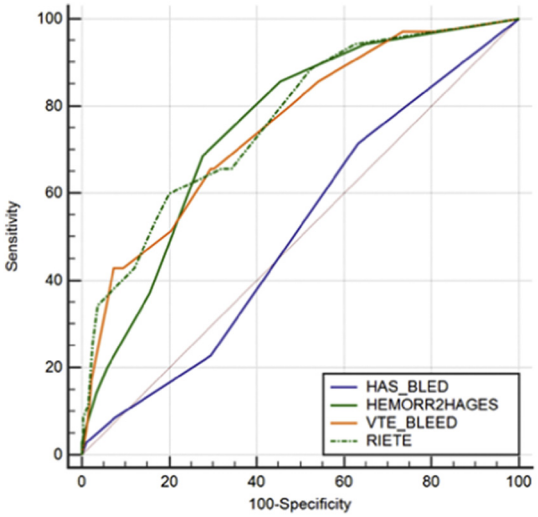

Fig. 3. Receiver operating characteristics curve for MB + CRNMB in regard to each of the compared bleeding risk scores. The AUC for HAS-BLED was 0.512 (95% CI 0.455–0.569), HEMORRHAGES 0.757 (0.700–0.799), VTE-BLEED 0.754 (0.702–0.801), RIETE 0.767 (0.716–0.813). Only the differences in the AUC for HAS-BLED vs other risk scores was statistically significant (HAS-BLED vs HEMORRHAGES and RIETE $p < .001$; HAS-BLED vs VTE-BLEED $p = .002$).

threshold of 5750 ng/ml may more accurately identify patients at risk of hemorrhagic complications who were previously classified in the low-risk of bleeding category. To the best of our knowledge, this is the first attempt at supplementing these bleeding risk scores with additional data on DD levels.

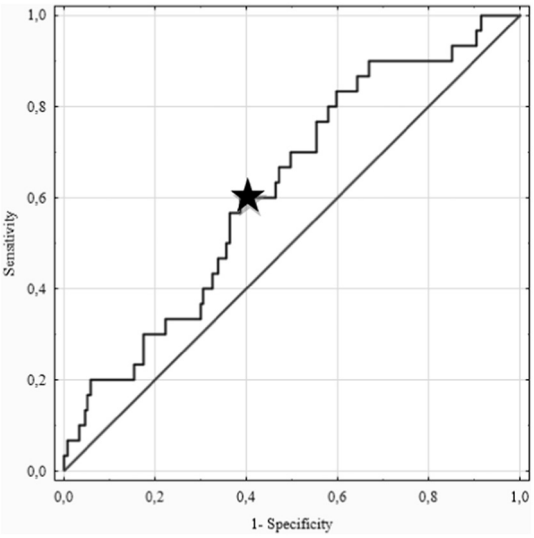

Fig. 4. Receiver operating characteristics curve for DD levels in regard to the occurrence of bleeding events. DD cut-off level of 5750 ng/ml is marked. The AUC was 0.621 (95% CI 0.520–0.721).

Table 5
Net reclassification improvement for bleeding risk prediction score and DD. Abbreviations: NRI- net reclassification improvement; SE- standard error.

Bleeding risk prediction score	NRI	SE; P
VTE-BLEED (< 2 points)	0.07	0.09; < 0.001
RIETE (≤ 4 points)	0.26	0.105; 0.01
$HEMORR_2HAGES$ (≤ 3 points)	0.30	0.100; 0.003
HAS-BLED (< 3 points)	0.28	0.117; 0.02

In our opinion, this study may have several potential clinical implications: better identification of patients at high risk of bleeding will allow for improved management regimens. In this study, we have observed the following: not only patients with high bleeding risk assessed with validated scores but also subjects with significantly elevated DD levels seem to be at increased bleeding risk and should be managed with special caution. They may especially benefit from tailoring the monitoring of treatment, more rigorous control of modifiable bleeding risk factors such as arterial hypertension, and shorter duration of the extended period of double antiplatelet therapy following percutaneous interventions. However, specific suggestions for daily clinical practice require further large, prospective studies.

This study is burdened by some limitations. We included consecutive patients managed in a single referral center, on all types of treatment, which may be also considered a strong point as it reflects the real-life nature of this study. Secondly, bleeding risk prediction scores were calculated retrospectively. It is noteworthy that the researcher responsible for score calculation was blinded to the patient outcome. A separate analysis of MBs and CRNMBs could be of value and should be verified in a larger patient population. The reclassification potential of DD could be strengthened by including a larger patient population. Lastly, both anticoagulant naïve and non-naïve patients were enrolled.

In conclusion, RIETE, HEMORR$_2$HAGES, and VTE-BLEED performed better at identifying APE patients in the acute phase of treatment at risk of in-hospital bleeding complications than the HAS-BLED score which showed no discriminatory ability. In this exploratory analysis, we show that augmenting existing bleeding risk scores with information on D-dimer levels may further increase their predictive capacity however, it should be strongly underlined that this requires further validation.

Declaration of Competing Interest

None.

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