



## Prediction and prognostic importance of in-hospital major bleeding in a real-world cohort of patients with pulmonary embolism<sup>☆</sup>



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### ABSTRACT

**Background:** Assessment of bleeding risk in patients with pulmonary embolism (PE) is challenging. Recently, the VTE-BLEED score was shown to predict major bleeding. Therefore, we aimed to investigate the VTE-BLEED score and assess the prognostic impact of major bleeding in a real-world cohort of PE patients.

**Methods:** Consecutive PE patients included in a prospective single-center cohort study between 09/2008 and 11/2016 were eligible for analysis; patients treated with thrombolysis were excluded. The VTE-BLEED was calculated post-hoc; in-hospital major bleeding was defined using the ISTH definition.

**Results:** Overall, 522 patients (median age 69, IQR 56–78 years; 53% female) were included in the present analysis; major bleeding occurred in 18 (3.5%) patients. A VTE-BLEED score  $\geq 2$  points identified patients at high-risk for major bleeding (OR 3.7, 95% CI 1.1–13.0, sensitivity 83%, specificity 42%). Additionally, a GFR  $< 30$  ml/min/1.73 m<sup>2</sup> (OR 6.0, 95% CI 1.8–19.8) and previous surgery (OR 3.6, 95% CI 1.4–9.3) were associated with major bleeding. A less frequent use of unfractionated heparin as initial treatment was associated with a decrease of major bleeding over time. Major bleeding was identified as strong predictor of in-hospital (OR 7.7, 95% CI 2.3–25.8) and 1-year mortality (HR 3.6, 95% CI 2.0–6.6), especially in normotensive patients (OR 12.1, 95% CI 3.5–43.0 and HR 6.0, 95% CI 2.9–12.6, respectively).

**Conclusions:** In a real-world cohort, the VTE-BLEED score identified PE patients at risk for in-hospital major bleeding. However, for assessment of bleeding risk, renal function and previous surgery should be considered. Major bleeding emerged as strong predictor of in-hospital and 1-year mortality.

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## 1. Introduction

Current guidelines recommend therapeutic anticoagulation of patients with pulmonary embolism (PE) for at least 3 months. Extended anticoagulation should be considered in patients with unprovoked PE based on their individual risk-to-benefit ratio including the assessment of bleeding risk [1,2]. However, most bleeding prediction scores available (such as the HAS-BLED) were developed for patients with atrial fibrillation and are of poor value for the prediction of short- [3] and long-term [4] bleeding complications in patients with venous thromboembolism (VTE). To address this topic, the *American College of Chest Physicians* (ACCP) provided a list of 18 risk factors derived from various cohort studies, and patients with at least two risk factors were

**Abbreviations:** AUC, area under the curve; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; OR, odds ratio; PE, pulmonary embolism; ROC, receiver operating characteristic; VTE, venous thromboembolism.

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considered to be at high risk for bleeding [2]. The recently proposed VTE-BLEED score, which was developed in the dabigatran arms of the pooled RE-COVER sister studies, identified six differently weighted variables (active cancer [2 points], males with uncontrolled hypertension [1 point], anemia [1.5 points], history of bleeding [1.5 points], age  $\geq 60$  years [1.5 points] and renal dysfunction [1.5 points]) as predictors of major bleeding in patients with VTE on stable oral anticoagulation receiving either warfarin or dabigatran [5]. Further, the VTE-BLEED score was externally validated in the HOKUSAI-VTE study in both, patients receiving warfarin or edoxaban [6]. A score of two or more points was associated with an odds ratio (OR) of 5.0 (95% confidence interval [CI], 3.5–7.1) and 4.0 (95% CI, 2.5–6.4) for bleeding complications in the pooled RE-COVER studies and the HOKUSAI-VTE study, respectively. However, a validation of the VTE-BLEED score in a real-world cohort of PE patients has not been performed thus far.

Furthermore, early (e.g. during the in-hospital stay) major bleeding constitutes a relevant complication and challenge in the management of patients with PE with a case fatality rate of up to 20% [7]. Major bleeding was identified as a predictor of short- and midterm-mortality in the *Rejestr ZATORowości płucnej w Polsce* (ZATPOL) and as a predictor of 1-year mortality in the *Registro Informatizado Enfermedad TromboEmbolica* (RIETE) [8,9]. However, the inclusion of patients receiving thrombolytic therapy in these two studies may have led to a higher incidence of both, bleeding and fatal events.

Therefore, the aim of our study was to validate the prognostic performance of the VTE-BLEED score in a real-world cohort of patients with PE, to identify predictors of in-hospital major bleeding and to investigate the impact of major bleeding on in-hospital and 1-year mortality.

## 2. Material and methods

### 2.1. Study design and patient cohort

Consecutive patients  $\geq 18$  years with confirmed acute PE were included in a single-center prospective cohort study (*Pulmonary Embolism Registry of Goettingen* [PERGO]) at the University Medical Centre Goettingen, Germany. The study protocol has been described in detail before [10,11]. Complete baseline data on clinical, electrocardiographic, echocardiographic, radiological and laboratory parameters were obtained using a standardized case report form.

As shown in Fig. A1 of the Supplementary material, patients were excluded for the following reasons: a) incomplete baseline data ( $n = 3$ ), b) treatment with thrombolysis or inclusion in the PEITHO study ( $n = 93$ ), c) inclusion in the AMPLIFY study ( $n = 1$ ) d) inclusion in PERGO more than once (only the first PE event was considered for analysis;  $n = 7$ ), e) treatment with surgical embolectomy or interventional approaches ( $n = 0$ ), f) subsegmental PE and other acute cardiac, respiratory or inflammatory disease responsible for symptoms and hemodynamic status on admission ( $n = 16$ ).

The VTE-BLEED and the HAS-BLED [12] score were calculated post-hoc for all patients, missing variables were considered to be normal.

All patients were followed for the in-hospital stay and 1-year survival status was assessed by consulting local registration offices. The primary study outcome was in-hospital major bleeding, the secondary study outcomes were in-hospital and 1-year mortality. Major bleeding was defined as fatal and/or symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in hemoglobin level of  $\geq 2$  g/dl or transfusion of  $\geq 2$  units of erythrocyte concentrates according to the definition of the *International Society of Thrombosis and Haemostasis* (ISTH) [13]. All events and causes of death were independently adjudicated by two of the authors (K.-P.K. and K.K.) blinded for the results of the bleeding prediction scores using medical records and autopsy records if available or by contacting the last treating physician; disagreement was resolved by a third author (M.L.).

The diagnostic and therapeutic management was in accordance with (at this time) current guidelines. All related decisions were left to the discretion of the treating physicians and were not influenced by the study protocol. Study results were not communicated to the clinicians and thus not used to guide patient management, or to monitor effects of treatment during the hospital stay or at any time during the 1-year follow-up period. The study protocol was conducted in accordance with the amended Declaration of Helsinki and was approved by the local independent Ethic Committee of the Medical University Goettingen, Germany; all patients gave written informed consent for participation in the study.

### 2.2. Statistical analyses

Categorical variables are expressed as absolute number or percentage and were compared using Fisher's exact test or Chi-squared test, as appropriate. Continuous variables did not follow a normal distribution when tested with the modified Kolmogorov-

Smirnov test (Lilliefors test); therefore, these variables are expressed as median with the corresponding interquartile range (IQR) and were compared using the unpaired Mann-Whitney  $U$  test. Receiver operating characteristic (ROC) curve analyses were performed to determine the area under the curve (AUC) of the VTE-BLEED and HAS-BLED score with regard to major bleeding. Further, the Hosmer-Lemeshow test was used to evaluate the difference between the predicted and observed risk estimates of the VTE-BLEED and HAS-BLED score. The prognostic relevance of dichotomous/dichotomized variables with regard to the primary and secondary study outcomes was assessed using univariable logistic regression analyses; results are presented as OR with corresponding 95% CIs. Additionally, parameters univariably associated with in-hospital mortality were separately tested in combination with major bleeding in multivariable logistic regression models. Kaplan-Meier analyses were used to compare the probability of long-term survival in different subgroups; the log-rank test was used to test for differences. Cox regression analyses were performed to test the prognostic relevance of dichotomous/dichotomized variables with regard to 1-year mortality; results are presented as hazard ratios (HR) with corresponding 95% CI. To identify independent predictors of 1-year mortality, significant predictors identified in univariable Cox regression analyses were included in a multivariable model using simultaneous selection. Scores containing variables already included in the multivariable model were excluded. For analysis of temporal trends, the study period was divided in four two-year segments (09/2008 to 08/2010, 09/2010 to 08/2012, 09/2012 to 08/2014 and 09/2014 to 11/2016). Testing for temporal trends was conducted using the Cochran-Armitage trend test for dichotomous/dichotomized variables.

A two-sided significance level of  $\alpha 0.05$  was defined appropriate to indicate statistical significance. Statistical analyses were performed using the SPSS software (IBM Corp. released 2016. IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp.).

## 3. Results

Of 642 patients included in PERGO between September 2008 and November 2016, 120 (18.7%) were excluded as described above and shown in Fig. A1 of the Supplementary material. Thus, 522 patients (median age, 69; IQR, 56–78 years; 53% female) were included in the present analysis. The baseline characteristics, comorbidities and initial findings of the study patients are presented in Table 1, left column.

During the in-hospital stay, 18 patients (3.5%) had major bleeding with a median time to event of 3 (95% CI, 2–15) days; of those, two were intracranial hemorrhages. No patient died due to bleeding. Patients with major bleeding had a longer median in-hospital stay (16; 95% CI, 10–28 vs. 9; 95% CI, 5–13 days  $p = 0.002$ ) and the prevalence of anemia, active cancer, recent surgery and severe renal impairment was higher compared to patients without major bleeding (Table 1, right columns).

At the time of the major bleeding event, 12 patients were treated with continuous unfractionated heparin (UFH; 67%), three were bridged from low molecular weight heparin (LMWH) to a vitamin-K antagonist (VKA; 17%) and one patient each was treated with LMWH (5.6%), VKA (5.6%) and argatroban (5.6%). Fig. A2 of the Supplementary material shows the initial anticoagulation and the incidence of major bleeding for each two-year segment of the study period. While the number of patients treated with continuous UFH decreased over time (77%, 73%, 50% and 39%;  $p < 0.001$ ), the number of patients treated with subcutaneous LMWH/fondaparinux increased (20%, 27%, 48% and 51%;  $p < 0.001$ ). In parallel with the less frequent use of continuous UFH, the incidence of UFH-associated major bleedings tended to decrease (2.7%, 3.7%, 3.3% and 1.4%;  $p = 0.457$ ) while the incidence of LMWH/fondaparinux-associated major bleedings remained stable at a low rate (0.9%, 0.9%, 0.0% and 0.7%;  $p = 0.624$ ).

### 3.1. Validation of the VTE-BLEED score

As shown in Fig. A3 of the Supplementary material, ROC analyses yielded an AUC of 0.69 (95% CI, 0.58–0.80) for the VTE-BLEED and of 0.58 (95% CI, 0.48–0.69) for the HAS-BLED score for prediction of major bleeding. Patients classified at high-risk ( $\geq 2$  points) by the VTE-BLEED score ( $n = 305$ ; 58%) had a major bleeding rate of 4.9% ( $n = 16$  events) compared to 1.4% ( $n = 2$  events) in patients classified at low-risk ( $n = 217$ ; 42%). This was associated with a sensitivity of 83% (95% CI, 61–94%) and a specificity of 42% (95% CI, 38–46%). Goodness of fit was satisfactory for the VTE-BLEED score ( $X^2 3.16$ ,  $p = 0.789$ )

**Table 1**  
Baseline characteristics, comorbidities and initial findings of 522 study patients.

	All study patients (n = 522)	Patients without major bleeding (n = 504)	Patients with major bleeding (n = 18)	p-Value
Age (years)	69 (56–78)	69 (56–78)	71 (60–78)	0.402
Age ≥ 60 years	361 (69)	346 (69)	15 (83)	0.298
Male sex	246/522 (47)	240/504 (48)	6 (33)	0.337
Risk factors for VTE				
Previous PE	62/521 (12)	61/503 (12)	1 (6)	0.710
Recent trauma <sup>a</sup>	16 (3.1)	16 (3.2)	0 (0.0)	0.566
Recent surgery <sup>a</sup>	100 (19)	92 (18)	8 (44)	<b>0.011</b>
Pregnancy/peripartum period	3 (0.6)	3 (0.6)	0 (0.0)	0.900
Contraceptive or sex hormone (replacement) therapy	39 (7.5)	39 (7.7)	0 (0.0)	0.385
Active cancer <sup>b</sup>	90 (17)	83 (17)	7 (39)	<b>0.022</b>
Unprovoked PE <sup>c</sup>	324 (62)	315 (63)	9 (50)	0.283
Comorbidities				
Arterial hypertension	334 (64)	321 (64)	13 (72)	0.619
Male with uncontrolled arterial hypertension <sup>d</sup>	84 (16)	82 (16)	2 (11)	0.751
Chronic pulmonary disease <sup>e</sup>	79/521 (15)	74/503 (15)	5 (28)	0.059
Chronic heart failure	85 (16)	82 (16)	3 (17)	1.000
Coronary artery disease	94 (18)	88 (18)	6 (33)	0.085
Previous stroke	49 (10)	48 (10)	1 (5.6)	0.482
Diabetes mellitus	87 (17)	86 (17)	1 (5.6)	0.333
Anemia <sup>f</sup>	199 (38)	188 (37)	11 (61)	<b>0.038</b>
Known liver disease <sup>g</sup>	15/411 (3.7)	15/393 (3.8)	3 (17)	0.567
Alcohol abuse	15/362 (4.1)	14/351 (4.0)	1/11 (9.1)	0.376
Previous bleeding	17/364 (4.7)	16/352 (4.6)	1/12 (8.3)	0.442
Laboratory values				
GFR ml/min/1.73 m <sup>2</sup>	72 (55–90)	72 (56–91)	48 (29–78)	<b>0.005</b>
GFR <60 ml/min/1.73 m <sup>2</sup>	160/502 (32)	151/486 (31)	9/16 (56)	0.051
GFR <30 ml/min/1.73 m <sup>2</sup>	30/502 (6.0)	26/486 (5.3)	4/16 (25)	<b>0.011</b>
hsTnT ≥14 ng/l	268/435 (62)	256/421 (61)	12/14 (86)	0.233
NT-proBNP ≥600 ng/l	188/387 (49)	178/375 (48)	10/12 (83)	<b>0.018</b>
Risk stratification				
Tachycardia (HR ≥ 100 bpm)	101/507 (20)	97/490 (20)	4/17 (24)	0.757
Systolic blood pressure <90 mm Hg	18/498 (3.6)	15/481 (3.1)	3/17 (17.6)	<b>0.020</b>
Hypoxia <sup>h</sup>	104/438 (24)	98/424 (23)	6/14 (43)	0.108
sPESI ≥1 point(s)	350 (70)	333 (66)	17 (94)	<b>0.010</b>
ESC risk classes				<b>0.009</b>
Low risk	85 (16)	85 (17)	0 (0.0)	
Intermediate-low risk	290 (56)	280 (56)	10 (56)	
Intermediate-high risk	123 (24)	118 (23)	5 (28)	
High risk	23 (4.4)	20 (4.0)	3 (17)	
Initial treatment				
Unfractionated heparin bolus	295 (57)	282 (56)	13 (72)	0.228
Continuous unfractionated heparin	300 (57)	286 (57)	14 (78)	0.092
Low molecular weight heparin or fondaparinux	200 (38)	197 (39)	3 (17)	0.081
Rivaroxaban	7 (1.3)	7 (1.4)	0 (0.0)	1.000
Apixaban	9 (1.7)	9 (1.7)	0 (0.0)	1.000
Other	6 (1.2)	5 (1.0)	1 (5.6)	0.789

Abbreviations: VTE denotes venous thromboembolism; PE, pulmonary embolism; GFR, glomerular filtration rate; hsTnT, high sensitivity troponin T; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; HR, heart rate; bpm, beats per minute; sPESI, simplified pulmonary embolism severity index; ESC, European Society of Cardiology.

Bold p-values indicate significant findings ( $p < 0.05$ )

<sup>a</sup> Within the past 4 weeks.

<sup>b</sup> Active or anti-tumor therapy within the last 6 months, or metastatic state.

<sup>c</sup> In the absence of a temporary or reversible risk factor such as surgery, trauma, immobilization, pregnancy/postpartum period, contraceptives or sex hormone replacement therapy according to the definition of the 2014 ESC guidelines [1].

<sup>d</sup> Male with initial systolic blood pressure ≥ 140 mm Hg.

<sup>e</sup> Bronchial asthma, chronic obstructive lung disease or interstitial lung diseases.

<sup>f</sup> Hemoglobin <13 g/dl in male and <12 g/dl in female patients.

<sup>g</sup> Defined as Child-Pugh B or C.

<sup>h</sup> Defined as oxygen saturation of <90% with or without oxygen administration.

while the HAS-BLED score overestimated major bleeding risk in higher risk classes (Fig. A4 of the Supplementary material). A VTE-BLEED score of ≥2 points was associated with a 3.7-fold increased OR for major bleeding during the in-hospital stay (Table 2). In comparison, the HAS-BLED score failed to identify patients at higher risk for major bleeding: 10 (3.7%) of 217 patients (42%) classified as high-risk had major bleeding compared to eight (3.2%) of 305 patients (58%) classified as low-risk. Concordantly, a HAS-BLED score >2 points was not able to predict major bleeding (OR, 1.1; 95% CI, 0.4–2.9).

Of the variables used for calculation of the VTE-BLEED score, only anemia, active cancer and a moderately impaired renal function (GFR < 60 ml/min/1.73 m<sup>2</sup>) were identified as univariable predictors

of major bleeding (Table 2). Besides those, previous surgery and a sPESI ≥1 point(s) were able to predict major bleeding and a severely impaired renal function (GFR < 30 ml/min/1.73 m<sup>2</sup>) emerged as the strongest predictor. The impact of initial anticoagulation on major bleeding events is shown and discussed in the Supplementary material.

### 3.2. Influence of major bleeding on short- and long-term mortality

Overall, 21 patients (4.0%) died during the in-hospital stay. Of those, 10 deaths were due to PE (48%), eight to cancer (38%), two to sepsis (9.5%) and one to recurrent PE (4.8%). Patients with major bleeding had a higher in-hospital mortality rate compared to patients without

**Table 2**  
Univariable predictors of in-hospital major bleeding.

	OR (95% CI)	p-Value
<b>Scores</b>		
VTE-BLEED $\geq 2$ points	3.7 (1.1–13.0)	<b>0.040</b>
sPESI $\geq 1$ point(s)	6.8 (1.3–36.2)	<b>0.025</b>
<b>Variables</b>		
GFR $< 60$ ml/min/1.73 m <sup>2</sup>	2.9 (1.1–7.9)	<b>0.038</b>
GFR $< 30$ ml/min/1.73 m <sup>2</sup>	6.0 (1.8–19.8)	<b>0.004</b>
GFR $-10$ ml/min/1.73 m <sup>2</sup>	1.4 (1.1–1.7)	<b>0.003</b>
Previous surgery <sup>a</sup>	3.6 (1.4–9.3)	<b>0.009</b>
Active cancer <sup>b</sup>	3.2 (1.2–8.6)	<b>0.019</b>
Anemia <sup>c</sup>	2.6 (1.0–6.9)	<b>0.048</b>

Abbreviations: OR denotes odds ratio; CI, confidence interval; sPESI, simplified pulmonary embolism severity index, GFR, glomerular filtration rate.

Bold p-values indicate significant findings ( $p < 0.05$ )

<sup>a</sup> Within the past 4 weeks.

<sup>b</sup> Active or anti-tumor therapy within the last 6 months, or metastatic state.

<sup>c</sup> Hemoglobin  $< 13$  g/dl in male and  $< 12$  g/dl in female patients.

major bleeding (22.2% vs. 3.6%,  $p = 0.005$ ) and major bleeding was associated with an elevated risk of in-hospital death (OR, 7.7; 95% CI, 2.3–25.8;  $p = 0.001$ ), especially in normotensive patients (OR, 12.1; 95% CI, 3.5–43.0;  $p < 0.001$ ). As shown in Table 3a, left column, active cancer was one of the strongest single predictors of in-hospital mortality. Accordingly, risk prediction scores including active cancer as a variable such as the VTE-BLEED score and the sPESI were able to predict in-hospital death, while scores not accounting for active cancer such as the HAS-BLED score (OR, 1.7; 95% CI, 0.7–4.1;  $p = 0.212$ ) failed. Predictors of in-hospital mortality in 499 normotensive patients are shown in Table 3a, right column. Of note, the prognostic value of major bleeding remained independent, both, in all study and in normotensive patients, if tested with each variable associated with in-hospital mortality separately in multivariable logistic models (data not shown).

**Table 3**  
a and b: Predictors of in-hospital and one-year mortality in all study and normotensive patients.

Variable	All study patients (n = 522)		Normotensive patients (n = 498)	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Major bleeding	7.7 (2.3–25.8)	<b>0.001</b>	12.1 (3.5–43.0)	<b>&lt;0.001</b>
VTE-BLEED $\geq 2$ points	7.6 (1.8–32.9)	<b>0.007</b>	6.2 (1.4–27.3)	<b>0.016</b>
Active cancer <sup>a</sup>	6.5 (2.7–15.6)	<b>&lt;0.001</b>	6.5 (2.5–17.1)	<b>&lt;0.001</b>
ESC per increase of risk class	2.6 (1.5–4.7)	<b>&lt;0.001</b>	2.7 (1.2–6.0)	<b>0.015</b>
sPESI $\geq 1$ point(s)	10.9 (1.5–81.8)	<b>0.020</b>	9.4 (1.2–71.3)	<b>0.030</b>
Syncope	3.3 (1.3–8.5)	<b>0.013</b>	1.7 (0.4–6.0)	0.439
NT-proBNP $\geq 600$ ng/l	4.0 (1.1–14.8)	<b>0.034</b>	6.3 (1.4–28.4)	<b>0.018</b>
<b>One-year mortality</b>				
	Univariable Cox regression analysis		Multivariable Cox regression analysis	
Variable	HR (95% CI)	p-Value	HR (95% CI)	p-Value
In-hospital major bleeding	3.6 (2.0–6.6)	<b>&lt;0.001</b>	3.2 (1.5–6.6)	<b>&lt;0.001</b>
VTE-BLEED $\geq 2$ points	3.6 (2.3–5.5)	<b>&lt;0.001</b>	–	–
HAS-BLED $> 2$ points	1.5 (1.1–2.1)	<b>0.013</b>	–	–
Active cancer <sup>a</sup>	5.5 (3.9–7.7)	<b>&lt;0.001</b>	9.1 (5.4–15.4)	<b>&lt;0.001</b>
Age $\geq 60$ years	2.1 (1.1–3.8)	<b>0.016</b>	1.4 (0.8–2.6)	0.277
Chronic heart failure	2.1 (1.5–3.1)	<b>&lt;0.001</b>	1.5 (0.8–2.6)	0.196
Coronary artery disease	1.6 (1.1–2.4)	<b>0.011</b>	1.5 (0.8–2.6)	0.195
Anemia <sup>b</sup>	2.1 (1.5–2.9)	<b>&lt;0.001</b>	1.3 (0.8–2.1)	0.195
ESC per increase of risk class	1.7 (1.4–2.1)	<b>&lt;0.001</b>	1.9 (1.3–2.8)	<b>0.001</b>
sPESI $\geq 1$ point(s)	9.4 (4.6–19.1)	<b>&lt;0.001</b>	–	–

Abbreviations: OR denotes odds ratio; CI, confidence interval; HR, hazard ratio; ESC, European Society of Cardiology; sPESI, simplified pulmonary embolism severity index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

Bold p-values indicate significant findings ( $p < 0.05$ )

<sup>a</sup> Active or anti-tumor therapy within the last 6 months, or metastatic state.

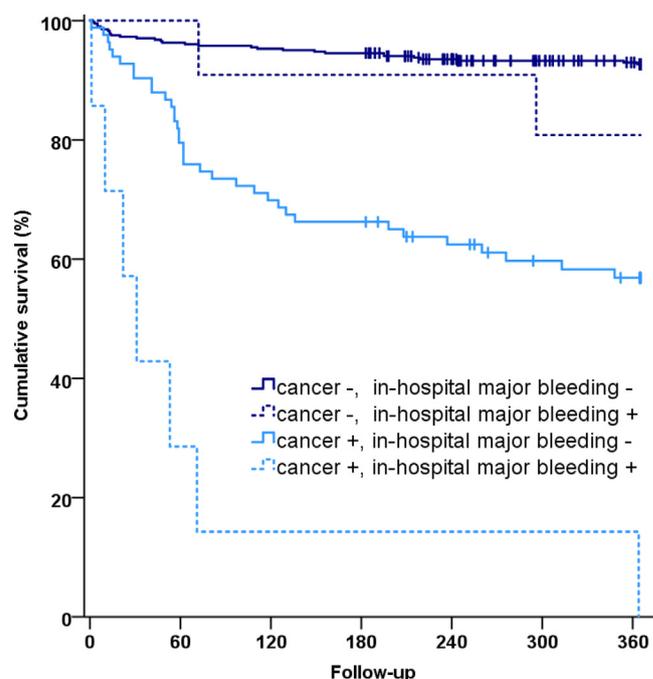
<sup>b</sup> Hemoglobin  $< 13$  g/dl in male and  $< 12$  g/dl in female patients.

One-year survival status was available for 502 patients (96%; median time of follow-up, 365; IQR, 323–365 days) and 73 patients (15%) died. Cancer was the leading cause of death ( $n = 35$ , 48%; cancer types are provided in Table A2 of the Supplementary material); further, 11 deaths were due to the initial PE (15%), nine to infectious disease (12%), seven to cardiac disease (9.6%), two each to recurrent PE (2.7%), pulmonary disease (2.7%), kidney disease (2.7%) and severe dementia (2.7%) and one to gastrointestinal bleeding (1.4%). Only two causes of death (2.7%) remained unknown. Of 18 patients with in-hospital major bleeding, as many as nine patients died during the observation period (1-year mortality rate, 50%); of those, five patients (56%) died due to cancer. As shown in Fig. 1, major bleeding was associated with a decreased probability of 1-year survival both, in patients with and without cancer. Of note, this was more pronounced in cancer patients with a 1-year case mortality rate of 100% (HR for major bleeding in cancer patients, 5.7; 95% CI, 2.5–13.0;  $p < 0.001$ ). Besides active cancer and other variables shown in Table 3b, left column, major bleeding was associated with an increased risk of 1-year mortality (HR, 3.6; 95% CI, 2.0–6.6;  $p < 0.001$ ); especially in normotensive patients (HR, 6.0; 95% CI, 2.9–12.6;  $p < 0.001$ ). In multivariable analysis, only active cancer, increase of ESC risk classes and in-hospital major bleeding were identified as independent predictors of 1-year mortality (Table 3b, right column).

## 4. Discussion

### 4.1. Prognostic value of the VTE-BLEED score

The occurrence of major bleeding is the most relevant and frequent complication of therapeutic anticoagulation and associated with substantial morbidity and mortality [7–9,14]. Since most bleeding events occur during the first weeks after treatment initiation [15], a score that identifies patients at high risk for in-hospital major bleeding may help to raise clinical awareness and to improve risk-adapted management such as anticoagulation quality control, blood pressure management and critical review of the concomitant use of platelet inhibitors and/or nonsteroidal anti-inflammatory drugs.



**Fig. 1.** Probability of 1-year survival in patients with/without active cancer and with/without in-hospital major bleeding.

In the present real-world cohort of patients with acute PE, we were able to demonstrate the prognostic value of the VTE-BLEED score to predict in-hospital major bleeding. A VTE-BLEED score  $\geq 2$  points was associated with a 3.7-fold increased risk for major bleeding and goodness of fit between observed and predicted rates of major bleeding was good (Fig. A4 of the Supplementary material). C-statistics and ORs of the VTE-BLEED score were comparable to those of the derivation and validation study [5,6]. Of note, compared to those, the present study included older patients with more comorbidities. Thus, as many 58% of patients were classified as high risk of bleeding based on the VTE-BLEED score compared to only 26% and 27% in the VTE-BLEED derivation [5] and the validation [6] study, respectively. In accordance, the prevalence of major bleeding of 3.5% in our cohort was higher compared to only 1.4% and 1.6% in the VTE-BLEED derivation [5] and the validation [6] study, respectively, but was comparable to those reported in other prospective registries (3.6% and 3.0%, respectively) [4,8,9].

#### 4.2. Predictors of in-hospital major bleeding

Both, in the VTE-BLEED derivation [5] and the validation [6] study, patients with cancer were underrepresented (4.4% and 2.6%, respectively). In contrast, in the present real-world cohort, as many as 17.2% of patients were diagnosed with active cancer. As expected, active cancer was associated with an increased risk for major bleeding. Accordingly, risk prediction scores including active cancer as a variable such as the VTE-BLEED score but also the sPESI were able to predict major bleeding (Table 2), while the HAS-BLED score (not accounting for active cancer) failed, as previously also shown by others [3,4].

The OR for major bleeding was twice as high for patients with a severely impaired renal function as compared to patients with a at least moderately impaired renal function (Table 2). As dabigatran is contraindicated in patients with severely impaired renal function ( $\text{GFR} < 30 \text{ ml/min/1.73 m}^2$ ), those patients were excluded from the RECOVER studies [16] and therefore not accounted for in the derivation of the VTE-BLEED score. Furthermore, patients with a high bleeding risk were excluded from the RECOVER studies; thus, patients who underwent previous surgery most likely were underrepresented. In contrast, in the present real-world cohort, previous surgery was associated with major bleeding, as also reported by others [2,17,18]. Therefore, if using the VTE-BLEED score for the assessment of bleeding risk, the prognostic impact of severe renal impairment and previous surgery might be underestimated and deserves further attention in clinical routine.

#### 4.3. Prognostic impact of in-hospital major bleeding on mortality

Major bleeding was identified as strong predictor of in-hospital and 1-year mortality, especially in normotensive patients (Table 3), and remained an independent predictor in multivariable analyses. These findings are in accordance with results from ZATPOL [8] and RIETE [9]: in ZATPOL, major bleeding (defined according to the definition of the ISTH) was an independent predictor of 30-day (OR, 3.5; 95% CI, 1.5–8.0) and 90-day (OR, 2.8; 95% CI, 1.3–5.9) mortality in 1112 unselected PE patients [8]. In 29,903 patients with VTE included in RIETE (of those, 14,590 patients [48.8%] with PE), major bleeding (defined as overt bleeding requiring transfusion of at least two units of blood cells, retroperitoneal, spinal, intracranial or fatal bleeding) was independently associated with death during (at least) 90-day follow-up (HR, 5.7; 95% CI, 5.0–6.3) [9]. However, patients receiving thrombolytic therapy were not excluded in these two studies which may have led to a higher incidence of both, bleeding and fatal events.

Interestingly, in the present real-world cohort, the case-fatality rate of bleeding was remarkable low: No patient died of bleeding during the in-hospital stay and only one patient (1.4%) during 1-year follow-up. In contrast, in 41,826 VTE patients included in RIETE, the case-fatality rate of bleeding was 19.7% (95% CI, 17.4–22.1%) during a mean duration of

7.8 months of anticoagulation (27,110 patient-years) [7]. In a meta-analysis summarizing data from 13 prospective cohort studies and 56 randomized controlled trials published until 2008 investigating 19,027 patients with VTE, the case-fatality rate of bleeding was 11.3% (95% CI, 7.5–15.9%) in the first three months of anticoagulation [7–9,14]. Thus, although in the present study major bleeding appears to reflect the importance of underlying diseases, the prognostic value of major bleeding to predict in-hospital and 1-year mortality remained independent from comorbidities in multivariable analyses. Therefore, the present study focuses not only emphasize the prognostic importance of major bleeding but also the clinical need for bleeding risk assessment tools such as the VTE-BLEED score to predict in-hospital major bleeding and allow for an improved clinical awareness and risk-adapted anticoagulation management.

A particularly relevant prognostic impact of major bleeding was observed in patients with cancer: no cancer patient with a major bleeding event during the in-hospital stay survived the first year after acute PE (Fig. 1). This finding is especially alarming since cancer increases both, the risk of major bleeding and of recurrent PE [19–21]. In the CATCH trial, anticoagulation with tinzaparin for 6 months compared to tinzaparin for 5 to 10 days followed by warfarin for 6 months was associated with a significant reduction of clinically relevant non-major bleedings (HR, 0.58; 95% CI, 0.40–0.84) in 900 VTE patients with cancer [22]. The HOKUSAI-VTE cancer trial demonstrated that edoxaban was noninferior to dalteparin with respect to the primary composite outcome of recurrent VTE or major bleeding (HR, 0.97; 95% CI, 0.70–1.36) although the rate of major bleeding was higher with edoxaban than with dalteparin (6.9% vs. 4.0%) [23]. Thus, the present study data support the current notion that all efforts should be made to prevent major bleeding events in PE patients with cancer. While anticoagulation with LMWH should be preferred over VKA treatment [1,2], further evidence is needed to evaluate which subgroup of PE patients with cancer has a favorable risk-to-benefit ratio for the treatment with NOACs (especially with regard to gastrointestinal bleedings).

#### 4.4. Limitations

Some potential limitations deserve consideration: First, patients were included at a single tertiary referral university center. Thus, the present study findings might be affected by local standards and resources and not generalizable to other settings. Second, therapeutic decision making was left to the discretion of the treating physicians. Thus, the type of initial anticoagulation and measures for anticoagulation quality control were not standardized. Third, although the prevalence of major bleeding in the present study was comparable to other prospective registries [4,8,9], the low number of major bleeding events precluded the performance of multivariable analyses and resulted in wide CIs of corresponding statistical findings.

## 5. Conclusion

In conclusion, in the present real-world cohort of patients with acute PE, the VTE-BLEED score was able to identify patients at risk for in-hospital major bleeding. However, in the assessment of bleeding risk in clinical routine, renal function and previous surgery deserve further consideration. Furthermore, in-hospital major bleeding was associated with an increased risk of in-hospital and 1-year mortality, especially in normotensive patients, emphasizing the need for reliable bleeding risk assessment tools such as the VTE-BLEED score to predict in-hospital major bleeding and allow for an improved clinical awareness and risk-adapted anticoagulation management.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.03.017>.

## Conflicts of interest

None of the authors reports a relationship with industry and other relevant entities – financial or otherwise – that might pose a conflict of interest in connection with the submitted article. The following authors report financial activities outside the submitted work:

Karl-Patrik Kresoja reports having received lecture honoraria from Bristol-Myers Squibb.

Matthias Ebner reports no relationships that could be construed as a conflict of interest.

Nina I. J. Rogge reports no relationships that could be construed as a conflict of interest.

Carmen Sentler reports no relationships that could be construed as a conflict of interest.

Karsten Keller reports no relationships that could be construed as a conflict of interest.

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