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Abstract: AIM OF STUDY Venous thromboembolic events (VTEs) are significant complications in patients with systemic malignancies. Thrombosis risk is poorly defined for patients with brain metastasis, and available risk calculation scores are not validated for these patients. METHODS We identified 811 patients with brain metastasis followed at our institution and reviewed electronic charts retrospectively for the occurrence of VTEs, along with candidate risk factors. Risk factors were tested in univariate and multivariate analyses and finally integrated in a score model for risk estimation. An independent cohort of 346 patients with brain metastasis was available for validation. RESULTS VTEs were documented in 97 of 811 patients (12.0%). Primary tumours with high thrombogenicity (p = 0.02, hazard ratio 1.7, 95% confidence interval (CI) = 1.1-2.8), dexamethasone (p = 0.011, hazard ratio 2.27, 95% CI = 1.5-4.5), chemotherapy (p = 0.005, hazard ratio 3.4, 95% CI = 1.6-7.5), body mass index > 35 kg/m^2 (p = 0.002, hazard ratio 3.4, 95% CI = 1.6-7.5) and immobilisation (p = 0.003, hazard ratio 2.4, 95% CI = 1.3-4.3) were confirmed to be independently associated with VTEs. We derived a score model for VTE risk estimation, the thrombogenic primary, immobilization, chemotherapy, obesity, steroid (PICOS) score (0-7 points). Receiver-operating characteristic curve analysis demonstrated its prognostic accuracy (area under the curve [AUC] = 0.71, 95% CI = 0.64-0.77), and its value for the evaluation of VTE risk was superior to that of other scores such as the Khorana (AUC = 0.51) or CONKO (AUC = 0.52) scores. The potential value of the PICOS score was confirmed in the validation cohort (AUC = 0.72, 95% CI = 0.63-0.82). CONCLUSIONS The PICOS score may become a helpful tool for the identification of patients with brain metastasis at high risk for VTEs and for stratification in controlled studies.

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Research Article

Venous thromboembolic events in patients with brain metastases: the PICOS score

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Abstract

AIM OF STUDY: Venous thromboembolic events are significant complications in patients with systemic malignancies. Thrombosis risk is poorly defined for patients with brain metastasis, and available risk calculation scores are not validated for these patients.

METHODS: We identified 811 patients with brain metastasis followed at our institution and reviewed electronic charts retrospectively for the occurrence of venous thromboembolic events, along with candidate risk factors. Risk factors were tested in uni- and multivariate analyses and finally integrated in a score model for risk estimation. An independent cohort of 346 patients with brain metastasis was available for validation.

RESULTS: Venous thromboembolic events were documented in 97 of 811 patients (12.0%). Primary tumors with high thrombogenicity (p=0.02, Hazard Ratio 1.7, 95% CI 1.1-2.8), dexamethasone (p=0.011, Hazard Ratio 2.27, 95% CI 1.5-4.5), chemotherapy (p=0.005, Hazard Ratio 3.4, 95% CI 1.6-7.5), BMI > 35 kg/m^2 (p=0.002, Hazard Ratio 3.4, 95% CI 1.6-7.5) and immobilization (p=0.003, Hazard Ratio 2.4, 95% CI 1.3-4.3) were confirmed to be independently associated with VTE. We derived a score model for venous thromboembolic event risk estimation, the **PICOS** (thrombogenic **P**rimary, **I**mmobilization, **C**hemotherapy, **O**besity, **S**teroids) score (0-7 points). Receiver Operating Characteristic Curve Analysis demonstrated its prognostic accuracy (AUC=0.71, 95% CI 0.64-0.77), and its value for the evaluation of venous thromboembolic event risk was superior to that of other scores such as the Khorana (AUC=0.51) or CONKO (AUC=0.52) scores. The potential value of the PICOS score was confirmed in the validation cohort (AUC=0.72, 95% CI 0.63-0.82).

CONCLUSIONS: The PICOS score may become a helpful tool for the identification of brain metastasis patients at high risk for venous thromboembolic events and for stratification in controlled studies.

Keywords: CNS, metastasis, venous thrombosis, prophylaxis, anticoagulation

Highlights

- Venous thromboembolic events (VTE) were found in 12% of our patients with brain metastasis (BM)

- **P**rimary, **I**mmobilization, **C**hemotherapy, **O**besity, **S**teroids (PICOS) are independently associated with VTE

- The PICOS score is superior to established risk models for VTE risk estimation

1. Introduction

Metastases to the central nervous system (CNS) are the most common malignant brain tumors [1] and their management is of major relevance with regard to the overall goal of cancer therapy of maintaining or improving quality of life [2, 3].

Cancer patients frequently suffer from vascular complications, mostly venous thromboembolic events (VTE) [4]. Potential risk factors for cancer-associated VTE include comorbidities, notably prior VTE, steroid medication, immobilization, and radiotherapy and chemotherapy [4-6]. Khorana *et al.* defined a score for risk estimation of VTE in cancer patients which takes into consideration site of cancer, increased platelet and decreased leukocyte count as well as decreased hemoglobin level and overweight. It is broadly used for clinical decision making towards thrombosis prophylaxis [6]. The Khorana score was further adjusted by replacing adipositas by Eastern Cooperative Oncology Group (ECOG) performance status (CONKO score [7]), or inclusion of serum markers (D-dimers and soluble P-selectin, Vienna CATS score [8]) or specification of chemotherapy (gemcitabine or platinum-based therapy, PROTECHT score [9]). However, none of these scores has been validated for patients with brain metastases (BM), and studies on several tumor entities have demonstrated the limitations of the Khorana score for risk estimation [10].

The management of VTE in BM patients has also remained controversial, both because of risk of hemorrhage upon institution of, and unclear benefit from, primary or secondary thrombosis prophylaxis and anticoagulant therapy [11, 12]. Retrospective studies report a limited risk of intracranial hemorrhage of BM patients on anticoagulation [13, 14], but prospective data in BM patients are lacking and current treatment recommendations for patients with BM [3] do not cover vascular complications in depth. Here, we sought to define the VTE risk profile of BM patients in a well-characterized discovery cohort of 811 as well as a validation cohort of 346 subjects and derive implications for VTE management.

2. Patients and methods

2.1 Patients

For the discovery cohort, patients diagnosed with and treated for BM were identified by review of the electronic chart system of the University Hospital Zurich (USZ). Interrogation of the electronic chart system (search term “brain metastasis”) yielded 1453 candidate adult patients, 811 patients with BM from solid tumors (patients with non-solid tumors, e.g. lymphoma, were excluded) were finally included (Figure 1). Follow-up was documented in the electronic chart, until death information was obtained in 628 of 811 BM patients (77.4%). Median follow-up of the remaining 183 of 811 patients (22.6%) which were later censored, was 15 months (95% CI 11-22). An external validation cohort of 346 patients from the University of Vienna was provided by authors ASB, RL and MP, data were collected according to local regulations. Follow-up until death was obtained for 231 of 346 patients (66.8%), median follow-up of the remaining 115 of 346 patients (33.2%) was 12.9 months (95% CI 10-18 months). This study was performed according to the Declaration of Helsinki and approved by the local cantonal ethics committee for the discovery cohort (KEK-ZH-Nr. 2018-00192) and for the validation cohort (Ethics number 1375/2018).

2.2 Variables

Vascular events were classified as thrombotic, including deep vein thrombosis (DVT), pulmonary embolism (PE), and cerebral venous thombosis (CVT) according to documentation in the electronic charts by the treating clinicians. The items of the Khorana score [6], primary tumor (very high risk: stomach, pancreas; high risk: lung, lymphoma, gynecologic, bladder, testicular, renal cell cancer (RCC), platelet (>350,000/μl) and leukocyte count (>11,000/μl), hemoglobin (<10 g/dl) levels as well as body mass index (BMI) >35 kg/m^2 and the ECOG performance status [15] were assessed at the time of BM diagnosis. Steroid intake was assessed at the time of BM diagnosis and 12 weeks later. Furthermore, data on other comorbidities and chemo- or radiotherapy after

diagnosis of BM, treatment with bevacizumab or immobilization by hemiparesis were captured in the discovery cohort. Severity grades of VTE were determined according to Common Terminology Criteria for Adverse Events (CTCAE) (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ docs/ CTCAE_v5_Quick_Reference_8.5x11.pdf) based on information from medical files.

2.3 Statistical methods

For univariate analysis, unpaired nominal data were assessed by the chi-square test and linearly scaled data by the Mann-Whitney U test where appropriate. To exclude bias from diverging survival, a stepwise Cox Hazard model with time to first VTE as outcome measure was applied for multivariate analysis of factors possibly associated with VTE, either identified in univariate analyses or previously described in the literature. Survival times were estimated using the Kaplan-Meier method. The items of the established Khorana and the CONKO score were integrated as possible confounding variables. The score model was further evaluated by assessment of the area under the receiver-operating characteristic (ROC) curves employing IBM SPSS statistics ®.
No discrimination is reflected by an area under the curve (AUC) of 0.5, a perfect discrimination by an AUC of 1, an AUC of 0.7 is widely accepted as threshold for a clinically relevant discrimination capability of a score [16]. The p-values in the ROC analysis test the null hypothesis for each score, whether the area under the curve really equals 0.50 (reference).
For comparison of scores, patients with missing data were omitted from respective analyses.
Statistical analysis was performed by authors FW and MCN using IBM SPSS statistics ®, Version 22 (IBM Co., Armonk, NY, USA) and GraphPad Prism software, version 7.0 (La Jolla, CA, USA).
Significance levels for two-sided p-values were set at $p<0.05$ for significant and $p<0.01$ for highly significant results.

3. Results

3.1 Co-factors and outcomes of VTE

Figure 1 shows the patient selection process, patient characteristics are summarized in Table 1 in the discovery cohort. Altogether, 12% of patients were diagnosed with at least one VTE after the diagnosis of BM, predominantly DVT and PE (Figure 2A). The median latency from diagnosis of BM to first VTE was 73 days (95% CI 41-126). The sequence of multiple VTE is outlined in Appendix A.

The risk for VTE was 6% (50 of 811 patients) within the first 3 months, 8% (61 of 811 patients) within 6 months, and 9% (74 of 811 patients) within one year after diagnosis of BM. VTE was detected within 24 h before diagnosis of BM in 2 of 811 patients, one of them with symptomatic DVT, one with asymptomatic PE.

Information on VTE prophylaxis prior to the first VTE was available for 91 of 97 patients; 82 patients (90%) had no prophylaxis at all. Two patients (2%) were already on oral anticoagulation with vitamin K antagonists due to prior diagnosis of atrial fibrillation and 7 patients (8%) were on prophylactic low weight molecular heparin (LWMH). After the first VTE, 17 of 82 patients (21%) with no prior prophylaxis received no further VTE treatment; 16 patients (20%) were placed on oral anticoagulants and 49 patients (59.8%) were placed on therapeutic dose LWMH. Before the second VTE, anticoagulation had been stopped in some cases: anticoagulation in 4 of 6 patients (67%) and therapeutic dose LWMH 5 of 11 patients (46%), probably because of perceived increased bleeding risk. In turn, one of three patients without prophylaxis after the first thrombosis was placed on LWMH after the second VTE.

In the discovery cohort, 568 of 811 patients were operated for BM. Of those, 75 experienced a VTE (13%), with no information on the exact date in 6 of 75 patients; in the remaining 69 patients, VTE occurred predominantly in the postoperative phase within 4 weeks or later (Figure 2B). Median latency from surgery to first VTE was 28 days (95% CI 10-82). Overall survival in the

discovery cohort was 11 months (95% CI 8.8-11.2 months). There was no difference between patients with (10 months, 95% CI 8.6-11.4 months) or without VTE (12 months, 95% CI 9.1-14.9 months; p=0.774, Log-Rank test). Symptoms from and outcomes of VTE are considered in Appendix B and Figure A.1. In the validation cohort, at least one VTE was diagnosed in 38 of 346 patients (11.0%) with up to four VTE after diagnosis of BM (see Table A.1 for patient characteristics). The rate of operated patients in the validation cohort was lower than in the discovery cohort (26.6% vs. 70.0%, Table1 and Table A.1).

3.2 Identification of risk factors for cancer related thrombosis in BM patients

The overall rate of VTE in the discovery cohort was 12% across all tumor types. The highest incidence was found for patients with cancer from unknown primary tumor (CUP, 24%), lung (13%) and RCC (21%) (Table 1). Patients with history of VTE prior to diagnosis of BM had a higher rate of VTE in the later course of disease (p=0.052, Table 1). There was a significant association between BM from CUP compared to other patients and risk of VTE (p=0.008, Chi-square test), but no association was found for patients with other primary tumors (Table 1). We then clustered tumor entities with higher (including CUP, lung carcinoma and RCC) and with lower VTE rates (melanoma, breast cancer, gastrointestinal cancer, other) from the discovery cohort. These associations of tumors and VTE rates were in line with previous reports [6, 17]. There was a significant difference in VTE rate between tumors with high (61 of of 406 patients, 15%) and low (36 of 405 patients, 9%) thrombogenicity (p=0.007, Chi-Square test).

On univariate analysis in the discovery cohort, begin or continuation of chemotherapy after diagnosis of BM was associated with VTE (p=0.000062, Table 1). Neither for radiotherapy to the brain (p=0.830) nor for treatment with bevacizumab (p=0.146) such association with VTE was observed (Table 1). There was a trend towards association of VTE and dexamethasone intake at the time of diagnosis of BM (p=0.063) and 12 weeks afterwards (p=0.052, Table 1). Furthermore, immobilization by e.g. severe hemiparesis or other neurological deficits was associated with VTE

(p=0.035, Table 1). Adipositas WHO grades at the time of diagnosis were not associated with VTE rate. We next performed an analysis of patients with WHO grade II and III adipositas since a BMI > 35 kg/m^2 has been reported to be associated with an increased VTE risk [6]. Such patients showed indeed a higher rate of VTE, albeit this subgroup was very small (p=0.006, Table 1).

In the validation cohort, percentages of patients with VTE were evenly higher in individuals exposed to the risk factors identified in the discovery cohort, although this was statistically not significant for all of them (thrombogenic primary tumor: p=0.061; immobilization: p=0.00001; chemotherapy: p=0.228; obesity: p=0.799; dexamethasone p=0.004; all Chi-square test; see also Table A1). For consideration on the effect of thrombosis prophylaxis in the discovery cohort see Appendix C.

We tested furthermore the diagnostic accuracy of the Khorana score [6] at the time of diagnosis of BM in the discovery cohort. Except for BMI > 35 kg/m^2 (p=0.006, Table 1), none of its items were associated with VTE risk (tumor histology: p=0.309, Chi-square test; TC: p= 0.579, LC: p=0.409, Hb: p=0.889, all Mann-Whitney U Test, data not shown) in univariate analysis. In multivariate analysis employing a Cox regression model, none of the score items showed an independent association with VTE risk (Table A.2). However, the Khorana score could be calculated for 498 of 811 patients and the CONKO score for 535 of 811 patients only in the discovery cohort.

3.3 Multivariate analysis

The items of the Khorana score and factors associated with the incidence of thrombotic events in univariate analysis were further explored in by a Cox Hazard model. Co-variates for VTE were high thrombogenic primary tumors, chemotherapy, dexamethasone intake at the time of diagnosis, immobilization, and high BMI (>35 kg/m^2). Primary tumors with high thrombogenicity (p=0.020, HR 1.7, 95% CI 1.1-2.8), dexamethasone intake (p=0.011, HR 2.3, 95% CI 1.5-4.5), chemotherapy

after diagnosis of BM (p=0.005, HR 3.4, 95% CI 1.6-7.5), BMI > 35 kg/m^2 (p=0.002, HR 3.4, 95% CI 1.6-7.5) and immobilization (p=0.003, HR 2.4, 95% CI 1.3-4.3) were confirmed to be independently associated with VTE in the discovery cohort (Table 2). In the validation cohort, immobilization (p=0.001, HR 6.2, 95% CI 2.7-14.2) and dexamethasone intake at the time of diagnosis (p=0.046, HR 2.3, 95% CI 1.1-5.0) were confirmed to be independently associated with VTE. A trend was shown for thrombogenic primary tumors (p=0.225, HR 1.7, 95% CI 0.7-4.3) and chemotherapy (p=0.146, HR 2.0, 95% CI 0.8-4.8). Only 14 patients with a BMI >35 kg/m^2 were available for evaluation, which limits the statistical analysis (p=0.448, HR 1.8, 95% CI 0.4-7.9, Table A.3).

3.4 Development of a new score for VTE risk estimation: the PICOS score

These factors that were independently associated with VTE in the discovery cohort were used to derive a model for VTE prediction. Scores were calculated according to HR values (HR<2 scores 1 point; HR=2-3 scores 2 points; HR>3 scores 3 points): dexamethasone intake 2 points, chemotherapy 1 point, thrombogenic primary 1 point, immobilization 2 points, BMI > 35 kg/m^2 3 points. The **PICOS** (thrombogenic **P**rimary, **I**mmobilization, **C**hemotherapy, **O**besity, **S**teroids) score could be calculated for 671 patients. Post-hoc testing revealed that the occurrence of VTE increased with the score result (Figure 3A,B). We next performed a Receiver Operating Characteristic (ROC) Curve Analysis to assess for sensitivity and specificity (Figure 3C). We found an AUC of 0.71 (95% CI 0.64-0.77, p=0.0000035), which reflects the power of our score. We then tested the PICOS score against the established Khorana and the CONKO score in the discovery cohort in the subgroup of patients for which all respective score items were available (n=372 of 811 patients). Here, we found an AUC of 0.69 (95% CI 0.60-0.78, p=0.000280) for the PICOS score compared to an AUC of 0.51 (95% CI 0.44-0.59, p=0.761) for the Khorana score or an AUC of 0.52 (95% CI 0.45-0.59, p=0.646) for the CONKO score (Figure 4). The discrimination capability of our score was significant for VTE within the first 3 months (AUC=0.65, 95% CI 0.56-0.73,

p=0.000010), 6 months (AUC=0.67, 95% CI 0.59-0.74, p=0.000010) and 12 months (AUC=0.67, 95% CI 0.61-0.73, p=0.00001, all ROC analysis in the discovery cohort), although AUC were just below the threshold of 0.7. Evenly, there was no significant difference between operated and non-operated patients in the discovery cohort (non-operated patients: AUC=0.704, p=0.01; operated patients: AUC=0.67, p=0.00007). In the validation cohort, we found an AUC of 0.72 (95% CI 0.63-0.82, p=0.000065, Figure 3D) for the PICOS score.

4. Discussion

Cancer-associated VTE are frequent in patients with systemic malignancies and associated with impaired quality of life and unfavorable outcome [4, 18]. In contrast to cancer patients with extracranial tumor load only [18, 19], the risk profile for VTE in BM patients is poorly defined. Here we provide data on the incidence of VTE in a well-defined cohort of 811 BM patients. We observed an overall VTE rate of 12% from diagnosis of BM until death in the discovery cohort and of 9% within the first year, whereas VTE incidence for patients with extracranial systemic cancer varies between 3% and 12% [20]. Findings in an independent external validation cohort (n=346 patients) were similar with a VTE rate of 11% from diagnosis of BM until death.

Our dataset suggests that the Khorana Thromboembolic Risk Score, a broadly applied tool for estimation of thrombosis risk in cancer patients [4] and its adapted version, the CONKO score, are not valid for BM patients. Only high BMI was associated with thrombosis, but not other score items (Table A.1). Notably, primary tumors for which Khorana et al. reported the highest thrombogenicity (pancreas and stomach cancer), were underrepresented here because they rarely cause BM [1]. The accuracy of scores for risk estimation, including the Khorana Score, in other independent patient data sets is limited and often fails confirmation in subgroups or specific cancer entities [21]. Therefore, the specific risk profile for VTE in BM patients warranted further investigation.

Exploration for other, BM-specific risk factors revealed a group of primary tumors (lung cancer, CUP, renal cell cancer), chemotherapy, immobilization and dexamethasone as independently associated with VTE (Table 1 and Table 2). Although the rate of patients with VTE was higher if

they were exposed to the risk factors identified in the discovery cohort, not all of them were statistically confirmed, probably because the multivariate analysis was underpowered due to the limited number of patients. This was mainly true for obesity, and its re-evaluation as a risk factor for VTE in BM patients should be subject of future investigations.

The association of CUP and thrombosis concurs with the rate of 10% of all cancer patients having a history of preceding VTE without other risk factor even years ago [22]. Other putative risk factors, including radiotherapy or administration of bevacizumab, were not associated with VTE here, however, the number of patients receiving bevacizumab was low.

In contrast to a previous study [23] which reported a thrombosis risk of 20% in the postoperative phase, the majority of VTE was not associated with surgery here. This might be explained by the lower rate of perioperative thrombosis prophylaxis in the latter study (53% of patients) [23] whereas prophylaxis was administered to at least 66.0% of our patients. As a limitation of our study, reporting on thrombosis prophylaxis during hospitalization in the discovery cohort was possibly incomplete in older files from our cohort, and the rate of thrombosis prophylaxis might have been even higher.

The improved OS of 11 months in the discovery cohort compared to studies from the late 1990s (e.g. 4.4 months [24]) might reflect the advance in therapeutic options of BM patients in the last two decades and may provide an explanation why we encountered more thrombotic events in the later course of the disease (Figure 2). Altogether, the impact of surgery and perioperative prophylaxis on VTE risk could not be definitively determined in our cohort.

Based on the results from multivariate testing in the discovery cohort (Table 2), we developed a score model for VTE risk estimation, the PICOS score, that accounts for dexamethasone therapy (2 score points), chemotherapy after diagnosis of BM (1 score point), immobilization (2 score points), BMI > 35 kg/m^2 (3 score points) and thrombogenicity of the primary tumor (1 score point) (Figure 3). Post-hoc calculation of this score confirmed a significant association with VTE for serial points in time. ROC analysis revealed an AUC of 0.71 in the discovery cohort and 0.72 in the

validation cohort, indicating a clinically significant discrimination capability of the PICOS score, superior to the Khorana and CONKO scores (Figure 4).

Limitations of our study include its retrospective nature, incomplete data for some items, and the over-representation of patients operated for BM in the discovery cohort which does not reflect the overall population of patients with BM. However, the rate of VTE and the prognostic accuracy of the PICOS score were confirmed in the validation cohort, in which only 26% of patients were operated.

Prospective controlled trials on primary thrombosis prophylaxis in BM patients would be needed to assess whether this might prevent VTE-associated hospitalization or mortality. However, BM patients are mostly excluded from clinical trials assessing thrombosis risk and prevention in cancer patients (e.g. [25]), despite growing evidence that even full anticoagulation therapy is safe [26].

Based on the findings from our analysis, we conclude that there are subgroups of patients with increased risk for thromboembolic events who might benefit from vigorous prophylaxis and, if necessary, anticoagulation.

Conclusions

VTE are frequent complications in BM patients and are associated with increased morbidity and hospitalization rates. Optimal management remains to be defined. We propose a score (PICOS) that was confirmed in an independent validation cohort and might help to identify patients with increased VTE risk. Prospective trials should test its value to stratify for VTE risk in BM patients which may allow the PICOS score to become a valuable and validated tool for clinical decision making.

Conflict of interest:

FW has received travel support from Roche.

ASB has research support from Daiichi Sankyo (≤ 10000€), Roche (> 10000€) and honoraria for lectures, consultation or advisory board participation from Roche Bristol-Meyers Squibb, Merck, Daiichi Sankyo (all < 5000€) as well as travel support from Roche, Amgen and AbbVie.

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Figure legends

Figure 1: Consort chart.

The consort chart shows the selection path for patients from the discovery cohort included in this study. The upper part documents the preselection process to identify all patients with BM from solid tumors and subjects excluded from further analysis. The lower part shows how many patients were included in our analysis.

Figure 2: Incidence of VTE and association with surgery.

A. The number of patients (y-axis) with the respective VTE (x-axis) are shown as bar plots for the discovery cohort. B. Patient numbers (y-axis) are shown for different time points after surgery for BM (x-axis). Stacked bar plots show absence (black) versus presence (grey) of VTE. ECT=other extracranial thrombosis; DVT=deep vein thrombosis; PE=pulmonary embolism; CVT=cerebral venous thrombosis.

Figure 3: The PICOS score for estimation of VTE risk.

A,B. Bar plots show the absolute number (A) and percentage (B) of patients (y-axis) and score results (x-axis) for the discovery cohort. The lower part of each stacked column (black) depicts patients without VTE compared to those with VTE in the upper part (grey part). C,D. The receiver-operating characteristic curves are shown for the PICOS score (dashed black line) for the discovery (C) and the validation (D) cohort. A reference line indicates an AUC of 0.5 (continuous black line). AUC and p values as well as the 95% CI are indicated.

Figure 4: Comparison of the PICOS score and other scores for estimation of VTE risk.

Receiver-operating characteristic curves are shown for the PICOS score, the CONKO score and the Khorana score for the discovery cohort. A straight reference line indicates an AUC of 0.5 (continuous black line). AUC and p values as well as the 95% CI as indicated.

Tables

Table 1: Patient characteristics stratified for absence versus presence of VTE in the discovery cohort.

The results of review of medical files are shown. The first column depicts the respective characteristics item, with main items in bold letters and sub-characters in normal letters. The second column shows overall values for all patients, values as indicated. Percentages for sub-items reflect their fraction compared to the whole entity of a main item. The third and fourth columns show the fraction of patients without and with VTE, marked in italic. Percentages refer to the fraction of patients with or without VTE for each item.

Table 2: Multivariate analysis on candidate risk factors for VTE in the discovery cohort.

The results of multivariate testing of candidate risk factors for VTE are shown, which were calculated employing a Cox Hazard model. The first column depicts the respective candidate factor, the second one the two-sided p-values, the third column the respective Odds ratios following 95% CI in the fourth and fifth column.

Supplementary material

Figure A.1: Outcomes of VTE in the discovery cohort.

A, B. The number of patients (y-axis) and the respective type of VTE (x-axis) are shown as bar plots. In A, stacked bar plots show the method that first detected the respective VTE: CT scan of the lung (black), duplex ultrasound (dark grey) or other diagnostic methods (e.g. CT of the brain for detection of CVT, dark grey). B shows accordingly the fraction of patients with symptomatic (black) or asymptomatic VTE (grey). C,D.. The number of patients (y-axis) and the respective number of VTE over time (x-axis) are shown as bar plots. In C, stacked bar plots show whether patients with new diagnosis or subsequent relapse of VTE were treated as outpatients (black) or inpatients (grey). In D, stacked bar plots show fractions of survivors (grey) versus indivduals with VTE-associated death (black) from new or relapsing VTE.

Table A.1: Patient characteristics stratified for absence versus presence of VTE in the validation cohort.

The results of review of medical files are shown. The first column depicts the respective characteristics item, with main items in bold letters and sub-characters in normal letters. The second column shows overall values for all patients, values as indicated. Percentages for sub-items reflect their fraction compared to the whole entity of a main item. The third and fourth columns show the fraction of patients without and with VTE, marked in italic. Percentages refer to the fraction of patients with or without VTE for each item.

Table A.2: Multivariate analysis on association between score items of the Khorana Score, the CONKO Score and VTE in the discovery cohort.

Association of items of the Khorana score [6] and VTE was tested in a multivariate a Cox Hazard model with time to first VTE as outcome measure. Column one shows the respective score items, the following columns adjusted two-sided p-values, odds ratios with 95% CI. BMI=body mass

index; primary=primary tumor; Hb=hemoglobin; TC=thrombocyte count; LC=leukocyte count; ECOG=Eastern Co-operative Oncology Group score.

Table A.3: Multivariate analysis on candidate risk factors for VTE in the validation cohort.

The results of multivariate testing of candidate risk factors for VTE are shown, which were calculated employing a Cox Hazard model. The first column depicts the respective candidate factor, the second one the two-sided p-values, the third column the respective Odds ratios following 95% CI in the fourth and fifth column.

Figure 1

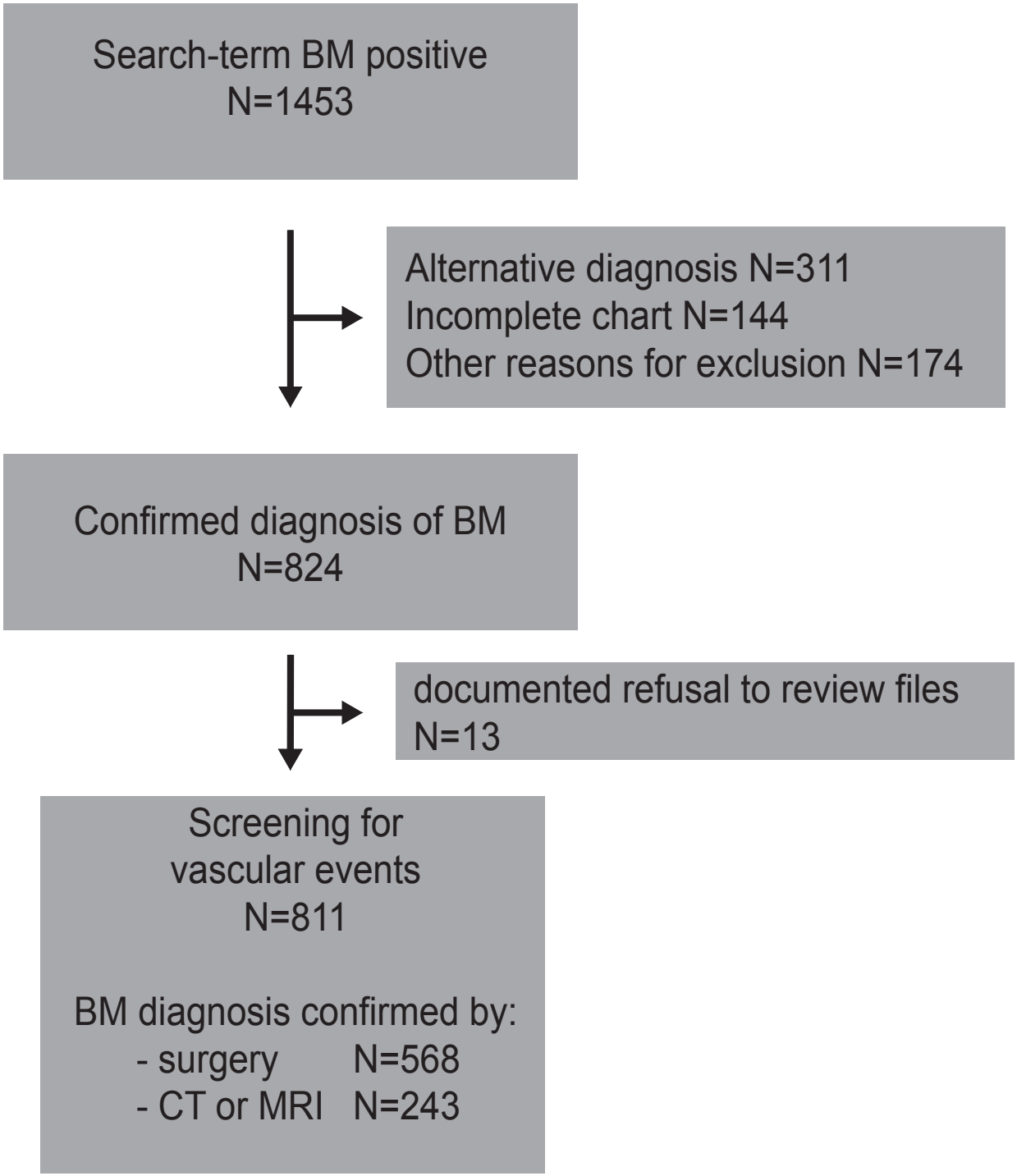

Search-term BM positive
N=1453
Alternative diagnosis N=311
Incomplete chart N=144
Other reasons for exclusion N=174
Confirmed diagnosis of BM
N=824
documented refusal to review files
N=13
Screening for
vascular events
N=811
BM diagnosis confirmed by:
- surgery N=568
- CT or MRI N=243

Figure 2

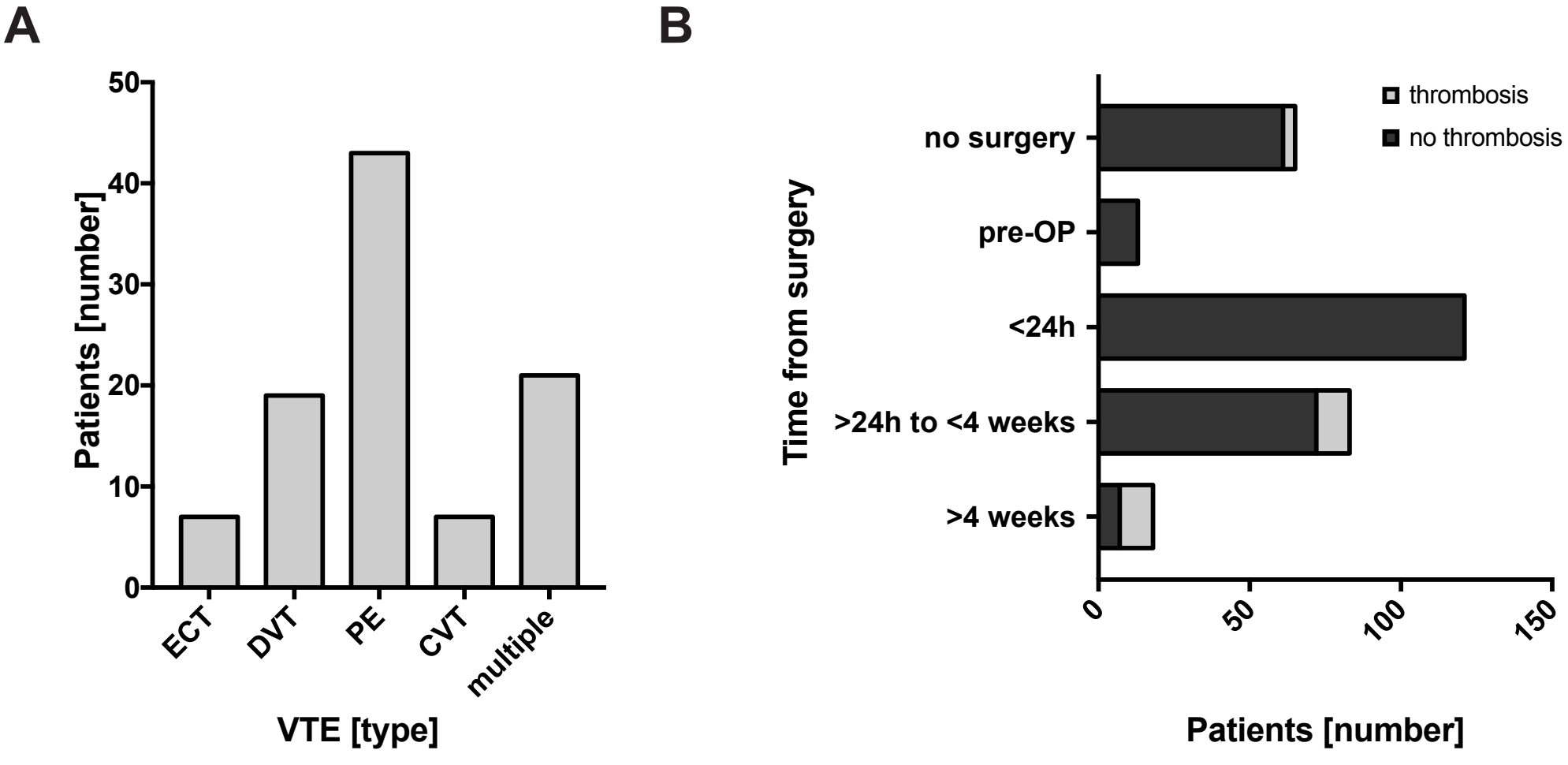
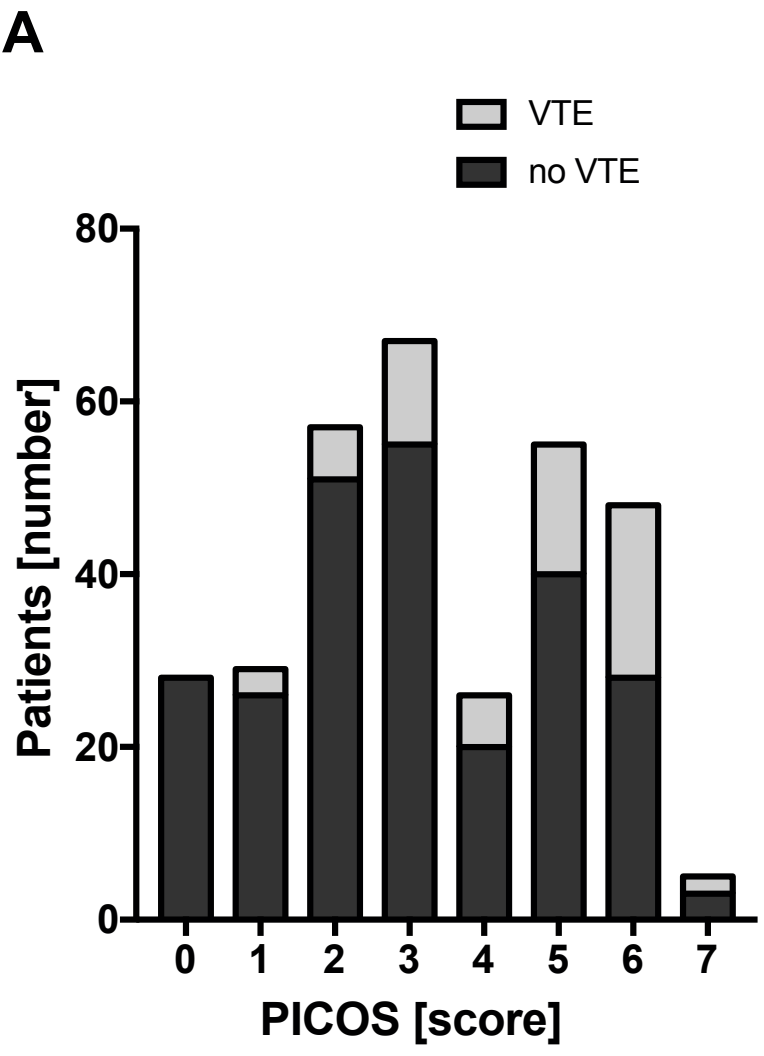
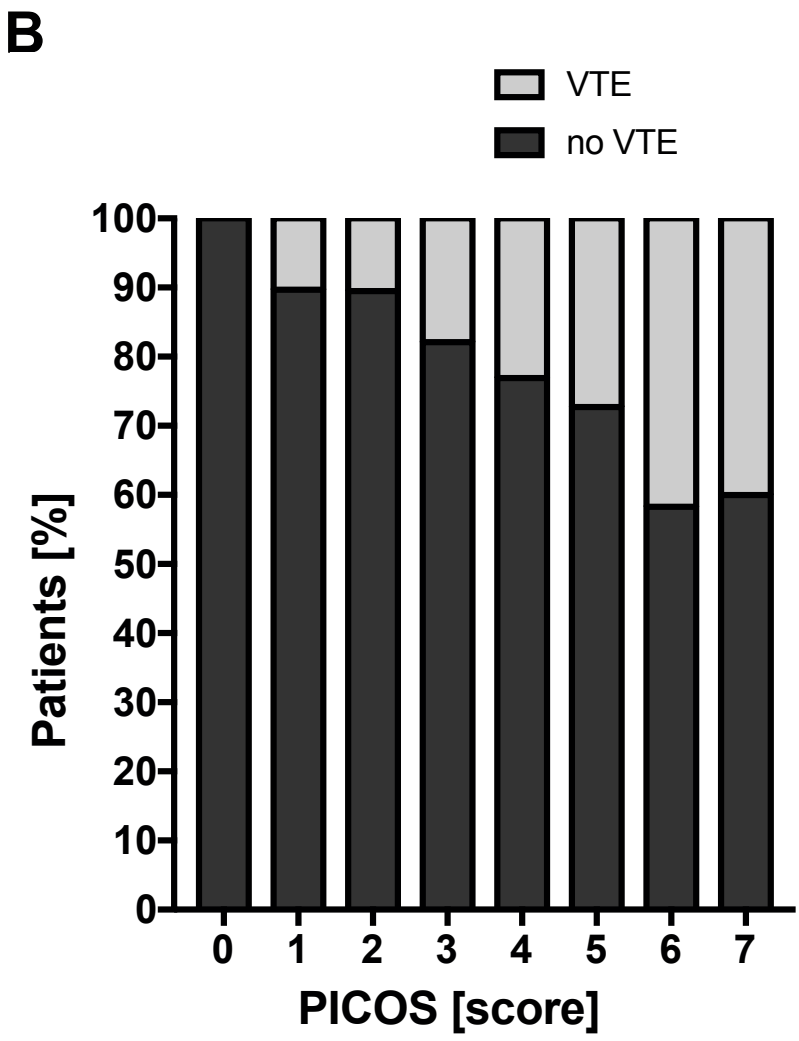

A
Patients [number]
50
40
30
20
10
0
ECT
DVT
PE
CVT
multiple
VTE [type]
B
thrombosis
no thrombosis
Time from surgery
no surgery
pre-OP
<24h
>24h to <4 weeks
>4 weeks
0
50
100
150
Patients [number]

Figure 3


A
VTE
no VTE
Patients [number]
80
60
40
20
0
0 1 2 3 4 5 6 7
PICOS [score]


B
VTE
no VTE
Patients [%]
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7
PICOS [score]

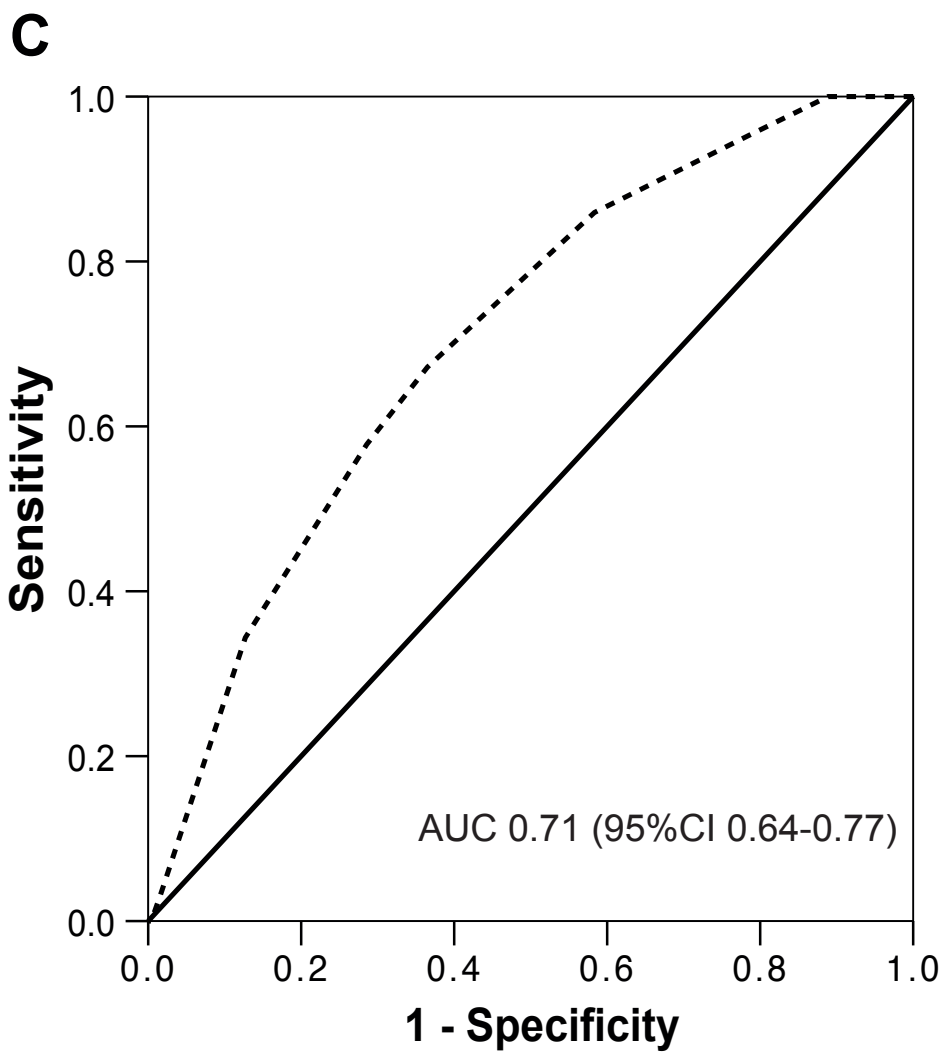

C
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0 0.2 0.4 0.6 0.8 1.0
1 - Specificity
AUC 0.71 (95%CI 0.64-0.77)

Figure 4

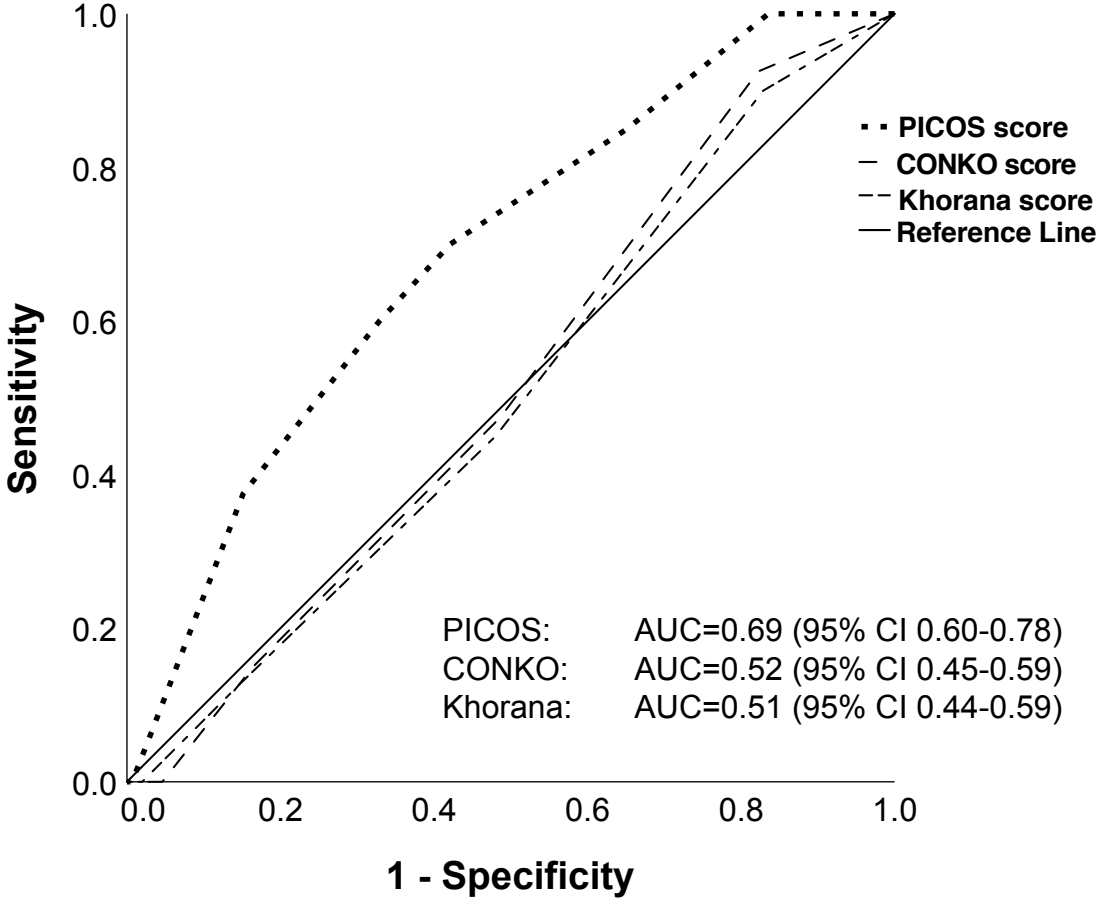

1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specificity
PICOS score
CONKO score
Khorana score
Reference Line
PICOS: AUC=0.69 (95% CI 0.60-0.78)
CONKO: AUC=0.52 (95% CI 0.45-0.59)
Khorana: AUC=0.51 (95% CI 0.44-0.59)

Table 1. Patient characteristics stratified for absence versus presence of VTE in the discovery cohort

	All patients (n=811)	No VTE (n=714, 88.0%)	One or more VTE (n=97, 12.0%)	p*
Sex (m/f)	428/383	374/340	54/43	0.543[a]
Age, median (range)	60.7 (19.3-90.1)	*60.8 (19.3-90.1)*	*59.7 (33.1-83.6)*	0.158[b]
Number of BM, median (range)	2 (1-64)	*2 (1-64)*	*2 (1-22)*	0.730[b]
KPS, median (range)	80 (40-100)	*80 (40-100)*	*80 (40-100)*	0.718[b]
Primary tumor, n (%)				
cancer of unknown primary tumor	45 (5.5)	*34 (75.6)*	*11 (24.4)*	**0.008**[a]
lung cancer	333 (41.1)	*289 (86.8)*	*44 (13.2)*	0.359[a]
melanoma	144 (17.8)	*133 (92.4)*	*11 (7.6)*	0.078[a]
breast cancer	100 (12.3)	*89 (89.0)*	*11 (11.0)*	0.752[a]
renal cell cancer	28 (3.5)	*22 (78.6)*	*6 (21.4)*	0.116[a]
gastrointestinal cancer	65 (8.0)	*59 (90.8)*	*6 (9.2)*	0.479[a]
other	96 (11.8)	*88 (91.7)*	*8 (8.3)*	0.243[a]
Prior vascular event, n (%)				0.617[a]
none	677 (83.5)	*75 (89.0)*	*75 (11.0)*	
ischemic stroke	13 (1.4)	*10 (76.9*	*3 (23.1)*	
subdural hematoma	2 (0.2)	*2 (100)*	*0 (0)*	
Intracranial hemorrhage	1 (0.1)	*1 (100)*	*0 (0)*	
deep venous thrombosis	28 (3.5)	*22 (78.6)*	*6 (22.4)*	
myocardial infarction	19 (2.3)	*16 (84.2)*	*3 (15.8*	
peripheral artery disease	25 (3.1)	*22 (88.0)*	*3 (12.0)*	
pulmonary embolism	14 (1.7)	*11 (78.6)*	*3 (21.4)*	
other vascular events	6 (0.7)	*6 (100)*	*0 (0)*	
multiple events	26 (3.2)	*22 (84.6)*	*4 (15.4)*	
History of VTE, n (%)				
no	769 (94.8)	*681 (88.6)*	*88 (11.4)*	Ref.
yes	42 (5.2)	*33 (78.6)*	*9 (21.4)*	0.052[a]
Smoking, n (%)				
no	250 (36.8)	*221 (88.4)*	*29 (11.6)*	Ref.
yes	429 (63.2)	*375 (87.4)*	*54 (12.6)*	0.705[a]
no information		*132*		
pack years (smokers only), median (range)	40 (1-100)	*40 (1-150)*	*40 (2-100)*	0.424[b]
Vascular prophylaxis at BM diagnosis, n (%)				0.107[a]
none	610 (75.3)	*547 (89.7)*	*63 (10.3)*	0.099[a]
acetylsalicylic acid	96 (11.9)	*78 (81.3)*	*18 (18.8)*	0.222[a]
clopidogrel	5 (0.6)	*4 (80.0)*	*1 (20.0)*	0.548[a]
acetylsalicylic acid+clopidogrel	11 (1.4)	*10 (90.9)*	*1 (9.1)*	0.764[a]
vitamin K antagonist	27 (3.3)	*23 (85.2)*	*4 (14.8)*	0.617[a]
new oral anticoagulant	9 (1.1)	*9 (100.0)*	*0 (0.0)*	0.271[a]
low weight molecular heparine	47 (5.8)	*40 (85.1)*	*7 (14.9)*	0.548[a]
antiplatelet drug + (new) oral anticoagluant	5 (0.6)	*2 (40.0)*	*3 (60.0)*	0.088[a]
incomplete file		*1*		
Brain irradiation after BM diagnosis, n (%)				
no	87 (11.2)	*76 (87.4)*	*11 (12.6)*	Ref.
yes	692 (88.8)	*610 (88.2)*	*82 (11.8)*	0.830[a]
incomplete file		32		
Chemotherapy after BM diagnosis, n (%)				
no	420 (52.0)	*388 (92.4)*	*32 (7.6)*	Ref.
yes	387 (48.0)	*322 (83.2)*	*65 (16.8)*	**<0.001**[a]
incomplete file		4		
Brain surgery after BM diagnosis, n (%)				
no	243 (30.0)	*220 (91.3)*	*21 (8.7)*	Ref.
yes	568 (70.0)	*493 (86.8)*	*75 (13.2)*	0.071[a]
Bevacizumab treatment, n (%)				
no	760 (95.5)	*673 (88.6)*	*87 (11.4)*	Ref.

yes	36 (14.5)	*29 (80.6)*	*7 (19.4)*	0.146 [a]
incomplete file		*15*		
Dexamethasone treatment, at diagnosis n (%)				
no	74 (9.6)	*70 (94.6)*	*4 (5.4)*	Ref.
yes	695 (91.4)	*606 (87.2)*	*89 (12.8)*	0.063 [a]
incomplete file		*42*		
Dexamethasone treatment, after 12 weeks n (%)				
no	173 (54.6)	*145 (83.8)*	*28 (16.2)*	Ref.
yes	144(45.4)	*108 (76.2)*	*36 (23.8)*	0.052 [a]
incomplete file		494		
Immobilization n (%)				
no	727 (89.6)	*646 (88.9)*	*81 (11.1)*	Ref.
yes	84 (10.4)	*68 (81.0)*	*16 (19.0)*	**0.035** [a]
WHO adipositas grades n(%)				
underweight (BMI<18.5 kg/m^2)	53	*47 (88.7)*	*6 (11.3*	0.980 [a]
normal (BMI 18.5-24.9 kg/m^2)	380	*338 (88.9)*	*42 (11.1)*	0.667 [a]
pre-adiopositas (BMI 25.0-29.9 kg/m^2)	183	*162 (88.5)*	*21 (11.5)*	0.956 [a]
adipositas grade I (BMI 30.0-34.9 kg/m^2)	64	*55 (85.9)*	*9 (14.1)*	0.882 [a]
adipositas grade II (BMI 35.0-39-9 kg/m^2)	13	*9 (69.2)*	*4 (30.8)*	0.110 [a]
adipositas grade III (BMI>40kg/m^2)	10	*7 (70.0)*	*3 (30.0)*	0.236 [a]
incomplete file		108		
BMI n (%)				
BMI<35 kg/m^2	680 (96.7)	*602 (88.5)*	*78 (11.5)*	Ref.
BMI>35 kg/m^2	23 (3.3)	*16 (69.6*	*7 (30.4)*	**0.006** [a]
incomplete file		108		

*Results of statistical testing, indicating p-values. Significant values are highlighted with bold letters, the respective statistical test is indicated with superscript letters. a = Chi square test; b = Mann-Whitney U test.

Table 2: Multivariate analysis on candidate risk factors for VTE*

Candidate factors	p=	Hazard Ratio	95% CI	
			Lower	Upper
BMI (>35 kg/m^2)	0.002	3.4	1.6	7.5
primary tumor (lung cancer, RC or CUP)	0.020	1.7	1.1	2.8
dexamethasone intake	0.011	2.3	1.5	4.5
chemotherapy after BM diagnosis	0.005	3.4	1.6	7.5
immobilization	0.003	2.4	1.3	4.3

* The results of multivariate testing of candidate risk factors for VTE are shown, which were calculated employing a Cox Hazards model. The first column depicts the respective candidate factor, the second one the two-sided p-values, the third column the respective Hazard Ratios following 95% CI in the fourth and fifth column.

Figure A.1

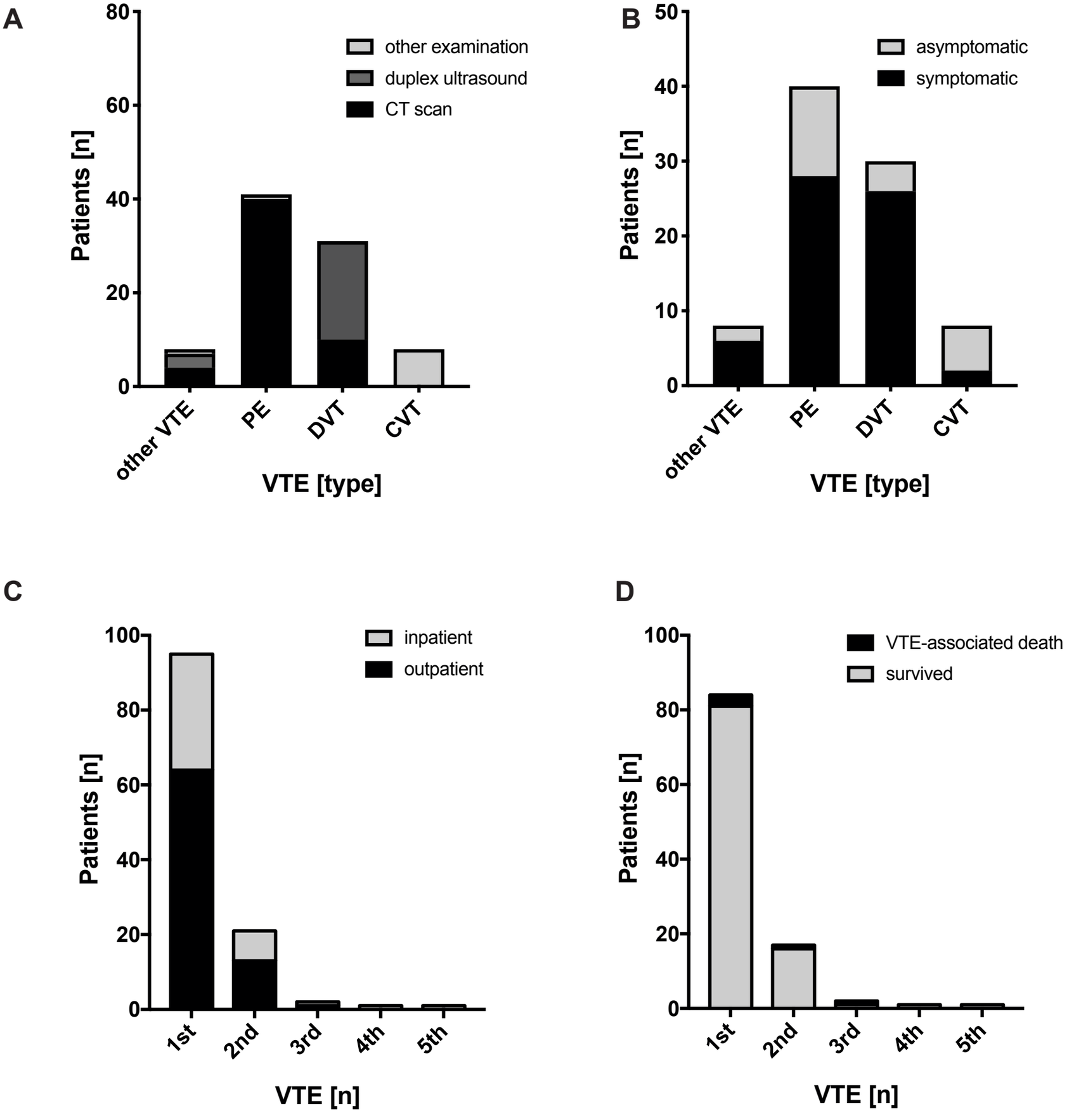

A
80
60
40
20
0
Patients [n]
other examination
duplex ultrasound
CT scan
other VTE
PE
DVT
CVT
VTE [type]
B
50
40
30
20
10
0
Patients [n]
asymptomatic
symptomatic
other VTE
PE
DVT
CVT
VTE [type]
C
100
80
60
40
20
0
Patients [n]
inpatient
outpatient
1st
2nd
3rd
4th
5th
VTE [n]
D
100
80
60
40
20
0
Patients [n]
VTE-associated death
survived
1st
2nd
3rd
4th
5th
VTE [n]

Table A.1. Patient characteristics stratified for absence versus presence of VTE in the validation cohort

	All patients (n=346)	No VTE (n=308, 89.0%)	One or more VTE (n=38, 11.0%)	p*
Sex (m/f)	178/168	*158/150*	*20/18*	0.877[a]
Age, median (range)	67.0 (27.7-91.7)	*67.3 (27.7-91.7))*	*64.7 (31.4-89.0)*	0.745[b]
Number of BM, median (range)	2 (1-15)	*2 (1-15)*	*2 (1-12)*	0.670 [b]
KPS, median (range)	80 (40-100)	*80 (40-100)*	*70 (30-100)*	0.331[b]
Primary tumor, n (%)				
cancer of unknown primary tumor	20 (5.8)	*13 (65.0)*	*7 (35.0)*	**<0.001** [a]
lung cancer	178 (51.4)	*159 (89.3)*	*19 (10.7)*	0.850 [a]
melanoma	57 (16.5)	*51 (89.5)*	*6 (10.5)*	0.904 [a]
breast cancer	63 (18.2)	*61 (96.8)*	*2 (3.2)*	**0.028** [a]
renal cell cancer	28 (8.1)	*24 (85.7)*	*4 (14.3)*	0.560 [a]
Thrombogenic primary (cancer of unknown primary tumor, lung or renal cell cancer), n (%)				0.061 [a]
no	120 (34.7)	*112 (93.3)*	*8 (6.7)*	
yes	226 (65.3)	*196 (86.7)*	*30 (13.3)*	
Brain irradiation after BM diagnosis, n (%)				
no	39 (11.3)	*32 (82.1)*	*7 (17.9)*	Ref.
yes	307 (88.7)	*276 (89.9)*	*31 (10.1)*	0.140 [a]
Chemotherapy after BM diagnosis, n (%)				
no	147 (42.7)	*135 (91.8)*	*12 (8.2)*	Ref.
yes	197 (57.3)	*173 (87.8))*	*24 (12.2)*	0.228 [a]
incomplete file		2		
Brain surgery after BM diagnosis, n (%)				
no	254 (73.4)	*225 (88.6)*	*29 (11.4)*	Ref[a]
yes	92 (26.6)	*83 (90.2)*	*9 (9.8)*	0.667 [a]
Dexamethasone treatment, at diagnosis n (%)				
no	218 (63.7)	*204 (93.6)*	*14 (6.4)*	
yes	124 (36.3)	*104 (83.9)*	*20 (16.1)*	**0.004** [a]
incomplete file		4		
Immobilization n (%)				
no	282 (81.5)	*261 (92.6)*	*21 (7.4)*	Ref.
yes	64 (18.5)	*47 (73.4)*	*17 (26.6))*	**<0.001** [a]
WHO adipositas grades n(%)				0.936 [a]
underweight (BMI<18.5)	17	*16 (94.1)*	*1 (5.9)*	
normal (BMI 18.5-24.9 kg/m2)	134	*117 (87.3)*	*17 (12.7)*	
pre-adiopositas (BMI 25.0-29.9 kg/m2)	97	*84 (86.6)*	*13 (13.4)*	
adipositas grade I (BMI 30.0-34.9 kg/m2)	35	*32 (91.4)*	*3 (8.6)*	
adipositas grade II (BMI 35.0-39-9 kg/m2)	7	*6 (85.7)*	*1 (14.3)*	
adipositas grade III (BMI>40kg/m2)	7	*6 (85.7)*	*1 (14.3)*	
incomplete file		49		
BMI n (%)				
BMI<35 kg/m^2	283 (95.4)	*249 (88.0)*	*34 (12.0)*	Ref.
BMI>35 kg/m^2	14 (4.7)	*12 (85.7)*	*2 (14.3)*	0.799
incomplete file		49		

*Results of statistical testing, indicating p-values. Significant values are highlighted with bold letters, the respective statistical test is indicated with superscript letters. a = Chi square test; b = Mann-Whitney U test.

Table A.2: Multivariate analysis on association between score items of the Khorana Score, the CONKO Score and VTE* in the discovery cohort

Items of the Scores *(Khorana et al. 2008)* *(Pelzer et al. 2008)*	**p=**	**Hazard Ratio**	**95%CI**	
			Lower	**Upper**
BMI	0.90	1.01	0.22	4.59
primary	0.70	1.09	0.69	1.74
Hb	0.52	1.39	0.51	3.76
TC	0.36	0.72	0.36	1.45
LC	0.56	1.17	0.68	2.03
ECOG	0.80	1.08	0.63	1.93

* Association of items of the Khorana score (Khorana et al., 2008) and VTE was tested in a multivariate a Cox Hazard model with time to first VTE as outcome measure. Column one shows the respective score items, the following columns adjusted two-sided p-values, Hazard Ratios with 95% CI. BMI=body mass index; primary=primary tumor; Hb=hemoglobin; TC=thrombocyte count; LC=leukocyte count; ECOG= Eastern Co-operative Oncology Group score.

Table A.3: Multivariate analysis on candidate risk factors for VTE in the validation cohort*

Candidate factors	p=	Hazard Ratio	95% CI	
			Lower	Upper
BMI (>35 kg/m^2)	0.448	1.8	0.4	7.9
primary tumor (lung cancer, RCC or CUP)	0.225	1.7	0.7	4.3
dexamethasone intake	0.046	2.3	1.1	5.0
chemotherapy after BM diagnosis	0.146	2.0	0.8	4.8
immobilization	0.001	6.2	2.7	14.2

* The results of multivariate testing of candidate risk factors for VTE are shown, which were calculated employing a Cox Hazards model. The first column depicts the respective candidate factor, the second one the two-sided p-values, the third column the respective Hazard Ratios following 95% CI in the fourth and fifth column.