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Prospective assessment of venous thromboembolism in lung cancer patients using a standardized screening protocol

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Abstract

Venous thromboembolism (VTE) is highly prevalent in cancer patients. While its actual incidence remains disparate among studies, specific subpopulations, such as lung cancer patients, might be at an increased risk. We aimed to assess the impact of a screening protocol in determining both the incidence and risk factors for VTE and evaluate the usefulness of predictive biomarkers and risk stratification tools in lung cancer patients. For this purpose, we designed a prospective cohort study including all consecutive, newly diagnosed lung cancer patients between October 2023 and April 2024 in a tertiary center and assessed each patient using a standardized screening protocol. VTE screening included baseline and 3-month reassessment of coagulation tests, D-dimer levels, and imaging (duplex ultrasound of the lower limbs for deep vein thrombosis screening and contrast-enhanced thoracic computed tomography for pulmonary embolism screening). A total of 102 patients were included, of which 16 (15.7%) were diagnosed with VTE. VTE was more frequent in males (p=0.031), patients with COPD (p=0.004), and patients with metastatic disease (p=0.038), particularly those under immunotherapy (p=0.026). Patients with VTE presented a D-dimer concentration more than three times higher at baseline and fivefold the levels observed in non-VTE patients at 3 months (p=0.002). Paired with Khorana scores, D-dimer concentration 4.5 mg/L at 3 months improved the predictive capacity of this VTE risk assessment tool in patients under active treatment. Active VTE screening yielded a significant increase in diagnosis, suggesting the incidence of this complication in newly diagnosed lung cancer patients is underestimated. Risk assessment tools can be enhanced by the addition of D-dimer-based parameters.

Key words: lung cancer, venous thromboembolism, screening, khorana, overall survival.

Introduction

Venous thromboembolism (VTE) is a major contributor to both higher morbidity and mortality in cancer patients [1-3], predominantly manifesting either in the form of deep venous thrombosis (DVP) and/or pulmonary embolism (PE). Multiple risk factors have been emphasized by international societies, ranging from age, body-mass index (BMI) or race to concomitant comorbidities. In addition to these non-cancer related factors, the primary malignancy site, histologic subtype and staging, as well as chemotherapy have all been associated with an increased risk of VTE [4].

The identification of robust biomarkers and oncogenic driver mutations has shifted the systemic treatment paradigm from "one-size-fits-all" towards a more tailored approach, introducing novel therapies such as tyrosine-kinase inhibitors and immunotherapy. Despite having very different action mechanisms, studies suggest both these treatment modalities can increase the risk of VTE [5]. While not necessarily undermining the overall survival (OS) and progression-free survival benefits observed in clinical trials, this warrants precaution in subpopulations at a particularly high risk of VTE-related mortality. Worldwide estimates of VTE incidence in cancer patients vary significantly; nevertheless, most studies agree that incidence is exceptionally high for lung cancer [6-9], ranging up to 21.2% in the first year after diagnosis [10]. The high heterogeneity between studies might be explained by only symptomatic events being reported, which could, in turn, mean that estimates of VTE-related mortality, while already demonstrated as significant for both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) might also be underestimated [10]. Multiple risk stratification models have been published; some of which, like the Khorana score, first developed in the context of solid tumors [11], have been integrated into clinical practice guidelines for the overall management of cancer-associated VTE [12,13]. Khorana is a predictive model firstly created to assess chemotherapy-associated thrombosis based on clinical and laboratory parameters that has, thus, been validated in multiple oncologic contexts. Nevertheless, the score seems less efficient at consistently differentiating high-risk from low-risk patients in cohorts with specific cancer subtypes and under novel therapies [14-16]. This has prompted multiple modifications to the base score model (PROTECHT [17], COMPASS-CAT [18]), with questionable degrees of improvement.

Our primary aim was to determine the overall incidence of VTE in newly diagnosed lung cancer patients using a standardized active screening protocol. Additionally, we aimed to determine how demographic features and both clinical and analytical factors might impact the incidence VTE and/or contribute to the active follow-up of these complications throughout treatment. Lastly, we aimed to compare the predictive capacity of different VTE risk

stratification scores in the specific context of lung cancer, and prospectively assess which model better correlates with active screening rather than symptom-driven diagnosis.

Materials and Methods

Prospective cohort study including patients with a novel diagnosis of lung cancer in a tertiary center between October 2023 and April 2024. Patients were enrolled after signing an informed consent provided after both complete staging and multidisciplinary tumor board decision regarding first-line treatment. There were no exclusion criteria other than the absence of informed consent. An inclusion form, comprised of complete demographic characterization, specific comorbidities disclosure (arterial hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, cerebrovascular disease, arterial peripheral disease, chronic kidney disease, COPD), smoking status and TVE risk factors (presence of central venous catheter, anti-hormonal therapy, major trauma or surgery 3 months, impaired mobility 7 days, pregnancy) was filled at baseline. Specific information regarding histology, staging (according to the 8th edition of the TNM classification for lung cancer), Programmed Death-Ligand 1 (PD-L1) expression, mutational status [using information provided by Next Generation Sequencing (NGS)] and performance status (according to the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) classification), as well as first-line treatment modality, was also included.

Aside from regular analyses and reassessment imaging related to standard follow-up, all patients were kept under active screening using specific blood sampling (coagulation tests; D-dimer serum concentration; complete blood count) and imaging (complete duplex ultrasound of the limbs and contrast-enhanced thoracic CT). Blood sampling and imaging were conducted at baseline before any cancer-related treatment, and three months after the first batch of exams. The Khorana and COMPASST-CAT risk scores for VTE were calculated for all patients (*Supplementary Table 1*). A modified Khorana score (mKhorana) was created with the addition of D-dimer serum concentration at 3-month reassessment, incorporating findings of this study regarding the independent relationship between increased VTE risk and elevated D-dimer concentrations.

The SPSS 28.0 package (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Normality in the distribution of variables was assessed using the Kolmogorov-Smirnov test. T-student and Mann-Whitney tests were applied for continuous variables and the chi-square test was used to compare categorical variables. The Phi Coefficient was used to quantify the strength of the relationship between two categorical binary variables. Receiver Operating Characteristic (ROC) curve analyses were employed to evaluate the performance of D-dimer serum concentration and different VTE risk stratification scores in distinguishing patients at

higher risk of VTE throughout follow-up; the accuracy of these risk scores was directly compared by determining the Area Under the Curve (AUC) of each predictive model. A binary logistic regression model was used to determine the potential association between VTE screening positivity and significant impact factors, including the aforementioned risk stratification models, while adjusting for possible confounders. Survival analyses were performed using Cox proportional hazard model.

Results

Overall demographics

A total of 102 patients were included in the screening program at the time of diagnosis. The majority of patients were male (63.7%), with a mean age of 67.8 ± 9.3 years old. All patients were Caucasian. Mean BMI was 24.7 ± 4.2 kg/m^2. Cardiovascular comorbidities, including hypertension, dyslipidemia or diabetes, were frequent (80.4%); specific comorbidities such as coronary heart disease (20% versus 0%; p=0.004) and arterial hypertension (78.5% versus 59.5%; p=0.041) were significantly more prevalent in male patients. Most patients were either active (30.4%) or former (46.1%) smokers; likewise, smoking was significantly more frequent in male patients (93.8% versus 45.9%; p<0.001). The median tobacco consumption of patients presenting a history of smoking was 46.5 (4; 120) pack-years. This translated into most concomitantly presenting COPD (65.4%; p=0.001). Other significant comorbidities and potential predisposing risk factors are discriminated in *Supplementary Table 2*.

The most frequent histologic subtype was lung adenocarcinoma (66.7%). Almost half the patients presented metastatic disease at diagnosis (45.1%). NGS detected mutations in two thirds of patients diagnosed with lung adenocarcinoma (66.7%) – the most frequent actionable mutations were EGFR (n=14), MET (n=6), ALK (n=4), BRAF (n=3) and HER2 (n=3).

Blood sampling and imaging screening tools

Blood samples and imaging results from each timeframe are described in Table 1. Sixteen patients (15.7%) were diagnosed with VTE during active screening, most of them at baseline (n=10; 62.5%). At baseline, the most frequent form of VTE was lower limb DVT (n=8; 80%); in the remaining 2 patients, screening was positive after the detection of PE during contrast-enhanced chest CT. Out of the 6 positive patients at 3-month screening, 4 (66.7%) were diagnosed with DVT and the remaining 2 with PE. Two patients diagnosed with VTE at baseline remained positive on the follow-up screening. All patients were asymptomatic at the time of diagnosis and were started on anticoagulation therapy. VTE was significantly more frequent in males (21.5% versus 5.4%; p=0.031), those with confirmed COPD (26.5% versus 5.7%; p=0.004) and in patients with more extensive oncologic disease (23.9% in metastatic disease

versus 8,9% in limited or locally advanced disease; p=0.038). Although slightly more prevalent in overweight/obese patients (BMI 30 kg/m^2), there was no statistically significant difference when compared with those presenting an average weight (BMI 18.5 to <25 kg/m^2) at baseline (19.6% versus 12.5%, respectively; p=0.329). Both NSCLC and SCLC patients presented similar rates of VTE (16.7% and 15.6%, respectively) and, while VTE was more frequent in lung adenocarcinoma patients (n=12; 17.6%) versus squamous cell carcinoma (n=2; 10%), the difference was not statistically significant (p=0.411). Twelve out of the 16 positive screening patients had undergone NGS; VTE was significantly associated with EGFR mutations (41.7%; p=0.048). Out of the total EGFR-positives, VTE was confirmed in 35.7% (n=5) of patients, an incidence rate surpassed only by ALK-positives (n=2; 50%).

All treatment modalities are described in Table 2. Patients submitted to systemic treatment with immune checkpoint inhibitors, either alone or in association with chemotherapy (n=33), presented significantly higher rates of VTE during active screening (27.3% positive screenings in the immunotherapy subgroup versus 10.1% in the non-immunotherapy subgroup; p=0.026). However, when adjusting for confounders such as cancer staging at diagnosis, immunotherapy failed to remain an independent predictor of VTE (p=0.401). Conversely, there were no positive screenings in the stereotactic body radiation therapy subgroup (p=0.051) and in the targeted therapy subgroup, although the latter comprised only 4 patients (p=0.581).

Using the standard normal range (0-0.50 mg/L) as reference, only a minority of patients presented normal serum D-dimer levels – the median D-dimer concentration in the overall sample was 1.33 mg/L (0.27-11.18) at baseline and 1.50 mg/L (0.27-13.00) at 3-months. Almost all patients with initially elevated D-dimer concentration maintained this elevation at the 3-month reassessment (95.7%; p<0.001). Coagulation was also altered in the majority of patients, but mostly due to increases in serum fibrinogen concentration [overall median 433 mg/dL (241-750) at baseline and 401 mg/dL (238-753) at 3-months reassessment]. The complete blood work analyses conducted in the context of the study are summarized and dichotomized according to screening results in Table 1. There was a statistically significant difference in D-dimer serum concentrations between patients with confirmed VTE and patients with a negative screening both at diagnosis and at 3-month reassessment (p=0.002), with the former presenting a D-dimer concentration more than three times higher at baseline and five-fold the concentration at the 3-month mark versus patients with no registered thromboembolic events.

VTE risk scores and outcome analysis

While the median Khorana risk score for the overall sample was 1 (1-3), 19.6% of patients were classified as high-risk (3) for VTE using this stratification tool. Khorana showed a

statistically significant correlation with positive screening in our sample (ϕ=0.262; p=0.008) – out of the 16 patients with a positive screening, 7 (35%) were predicted as high-risk for VTE using this score. The median COMPASS-CAT risk score for the overall sample, on the other hand, was 9 (4-13); 78.4% patients were classified as high-risk for VTE. While almost all patients with a positive screening were included in COMPASS-CAT's high-risk subgroup (n=15; 93.8%), this alternative score did not show a statistically significant correlation with positive screening for VTE (p=0.105). These scores failed to present a statistically significant correlation between each other for the overall sample (p=0.307) and when specifically targeting patients with limited or locally advanced disease (p=0.867); however, in the metastatic disease subgroup, there was a negative, statistically significant correlation between them: while 80% of COMPASS-CAT's low-to-intermediate risk patients were classified as high-risk using Khorana's criteria, less than a quarter (24.4%) of those in COMPASS-CAT's high-risk for VTE were considered high-risk by the Khorana score (p=0.011). Using a logistic regression model including potential confounders such as age, sex and serum D-dimer concentration levels at baseline, although there was a trend towards significance, the Khorana VTE risk class failed to remain a statistically significant predictor of a positive screening (p=0.096). Conversely, baseline D-dimer concentration [OR 1.29 (95%CI 1.01-1.68); p=0.05] and male sex [OR 7.69 (95%CI 1.22-48.53); p=0.03] were independent predictors of VTE in this population. When using the same regression model but pooled with the 3-month serum D-dimer concentration instead of baseline values, all three variables remained independent predictors of VTE in our sample (Table 3).

D-dimer serum concentration at baseline and at 3-month reassessment maintained an incremental correlation with the likelihood of confirmed VTE during active screening (*Supplementary Figure 1*). Using a ROC curve analysis with screening positivity as endpoint (Figure 1), both baseline and 3-month D-dimer concentrations showed adequate discriminative ability in predicting any-type VTE (AUC 0.746 and 0.741 respectively; p=0.002). At the optimal overall cutoff point, the model achieved a sensitivity of 69% and specificity of 67% using a cutoff value of 1.85 mg/L for baseline D-dimer concentration and a sensitivity of 75% and specificity of 63% using a cutoff value of 1.54 mg/L for the 3-month reassessment. When considering the optimal specificity cutoff point, the proposed D-dimer concentration values change to 2.40 mg/L for baseline assessment (56% sensitivity, 77% specificity) and 4.50 mg/L for the 3-month reassessment (56% sensitivity, 82% specificity). Paired with baseline Khorana scores in a modified post-treatment risk stratification model for VTE, D-dimer concentration 4.5 mg/L at 3-months improved the statistical power of the predictive model as an independent predictor of screening positivity. The mKhorana score remained an independent predictor of VTE (Table 4) regardless of age, sex, BMI, smoking

history, concomitant cardiovascular diseases, concomitant COPD, cancer histology and staging at diagnosis [OR 16.54 (95%CI 2.64-103.83); p=0.002].

Overall mortality was 17.6% (n=18); median OS for the deceased subgroup was 14 weeks (1-24). Patients presenting any-type VTE had significantly higher mortality rates than negative screening patients (56.3% versus 10.5%; p<0.001). Deceased patients also demonstrated significantly higher D-dimer concentrations (median 3.9 mg/L at baseline and 6.2 mg/L at 3-months versus 1.2 mg/L and 1.3 mg/L, respectively; p<0.001). D-dimer levels were an independent predictor of worse OS irrespective of confirmation of VTE both at baseline [HR 1.25 (95%CI 1.08-1.45); p=0.003] and at 3-month reassessment [HR 1.21 (95%CI 1.04-1.40); p=0.012]. Other blood workup analyses, including hemoglobin concentration (p<0.001) and total leucocyte counts (p<0.001) were also significantly altered in the deceased subgroup (see *Supplementary Table 3*).

Discussion

VTE in the context of oncologic disease is a direct consequence of a generalized hypercoagulable state, a hallmark of cancer [2,19]. Like more recent studies, our analysis suggests the incidence of VTE in lung cancer patients is underestimated.

In patients under active treatment, the incidence of VTE was reported by Connolly et al to be as high as 13.9% during a median follow-up period of 12 months [20]. Conversely, the prevalence of VTE in ambulatory patients with lung cancer was reported as 6.1% by Kuderer et al. [14], and 4.8% by Joshi et al. [21]. Despite prospectively designed, these studies did not actively screen for VTE, rather reporting on the prevalence of symptomatic episodes. One of the few prospective studies to have screened all included subjects for VTE showed an overall prevalence of 13.2% [22]. With a cumulative incidence of 15.7% during the first 3 months of active screening, our study aligns with this significantly higher rate than previously reported. A high rate of asymptomatic disease was also reported by Zhang et al. [22]; given the increasing reports on VTE as an independent predictor of mortality [10,23-26], this should raise questions regarding the importance of screening.

Due to the design of the protocol, routinely implementing a similar VTE screening program is both feasible and virtually inexpensive. Since the chosen timings overlap with treatment imaging re-evaluation recommendations, the added burden stems only from the addition of duplex ultrasound of the limbs for DVT screening. The cost-effectiveness of screening is corroborated by other studies that have also reported on the feasibility of such protocols; in one study by Muthu et al. [27], screening was able to detect 27% more cases of PE than symptom-based testing. One significant difference between our protocol and the one described in this study is the fact that PE was screened using CT with pulmonary angiography. In our

opinion, a contrast-enhanced CT-based protocol may further decrease costs, since it is the preferred imaging modality at initial evaluation of lung cancer patients. Nevertheless, pulmonary angiography remains the gold-standard for PE assessment, and although both are considered contrast-enhanced techniques, differences in image acquisition timings might result in an underestimation of PE incidence with non-angiography protocols.

While cancer histology did not show a relationship with VTE incidence, metastatic disease, EGFR-positive and immune checkpoint inhibitor treatment subpopulations displayed significantly higher rates of thromboembolic events. Mutational status and its association with VTE, in particular, has been the focus of different studies, most suggesting an association with EGFR mutations and ALK rearrangements, similarly to our study [28]. Although well-established in the context of chemotherapy [11,29], more recent studies have also reported higher incidence rates in patients treated with immunotherapy, with nearly one-fourth of all individuals developing VTE [30]. Despite failing to remain statistically significant when considering disease staging at diagnosis, we believe this to be worthy of future consideration, as standard-of-care treatments evolve towards an increase in immune checkpoint inhibitor usage throughout all cancer subtypes and, specifically, lung cancer.

Laboratory findings in our study were significantly correlated with the risk of VTE. Specifically, D-dimer serum concentration was significantly elevated in the overall study population and associated with higher incidence of events. Plasma D-dimer is the lysis end-product of crosslinked fibrin protein degradation and an indicator of coagulation dysfunction [31]. Since activation of coagulation and fibrinolysis is usually associated with most malignant tumors [32], oncologic disease has a direct effect over the hemostatic system [33]. However, despite the generalized hypercoagulable state seen in cancer patients, not all will develop thromboembolic events – moreover, as we have reported, even patients who did not present any VTE throughout follow-up still presented mostly elevated D-dimer serum concentrations. Lee et al. described how D-dimer tests are less valuable in cancer patients because of a lower negative predictive value than in noncancer patients as a consequence of the higher prevalence of DVT [34]. A proposed workaround is to increase the reference values for D-dimer levels in this population. This has previously resulted in an increase in specificity in both a study by Douma et al. [35] and Righini et al. [36], although there is currently no consensus regarding a cancer-specific cutoff standardization. While still lower than the median values observed in our study (1.33 mg/L at baseline and 1.50 mg/L at the 3-months re-evaluation), the cutoff of <1 mg/L (double the standard reference value) proposed by Chen et al. seems far more adjusted to our reported findings [37,38].

The high mortality attributed to cancer-associated VTE has led to the development of multiple risk stratification scores in an effort to predict which patients are at a higher risk and could

benefit the most from anticoagulant prophylaxis [27,39,40]. While symptomatic VTE is unquestionably more relevant in terms of OS, unsuspected VTE has also been associated with a worse prognosis[23,26]. The ASCO Clinical Practice Guideline [3] advocates for risk assessment using the Khorana risk score both initially and periodically thereafter, particularly when starting systemic therapy or in case of hospitalization. However, multiple studies have pointed towards a loss of its utility in the context of lung cancer [41,42]. This led to the development of both modified Khorana scores and alternative scoring systems altogether – a major focal point of different modified scores is the inclusion of D-dimer levels [43,44]. While our study demonstrated the original Khorana score has an adequate predictive capacity for VTE in the context of lung cancer, D-dimer serum concentration was still a better predictor of thromboembolic events, both at baseline and at the 3-month reassessment. A major shortcoming attributed to Khorana is that it fails to provide updated information on VTE throughout treatment; additionally, the score does not account for histology, genetic profiling or novel therapeutic modalities. To the best of our knowledge, ours is the first study to modify the original Khorana risk assessment tool by adding under-treatment D-dimer levels. The inclusion of a dynamic factor can increase the specificity of the original predictive model in the context of lung cancer, as we have demonstrated. Moreover, elevated D-dimer levels were an independent predictor of mortality regardless of screening status. This has been the subject of previous papers that signaled its potential as a biomarker in lung cancer [32]. Despite the lack of recommendations regarding the benefits of D-dimer-oriented prophylactic anticoagulation, we believe its inclusion as a complementary factor can enhance predictive models and possibly better tailor prophylaxis in the context of primary tumors for which current risk assessment tools have underperformed, such as in lung cancer.

Our study is limited by the small sample size obtained from a single center. This limits potential conclusions regarding genetic profiling and treatment-specific VTE risk assessment. Nevertheless, a major strength lies in the fact that all consecutive newly-diagnosed patients that agreed to participate were prospectively screened according to the same standardized protocol and pre-determined timepoints. Thus, we believe this accurately represents real-world data regarding the relationship between lung cancer and VTE. Because the screening protocol encompasses cost-effective, widely available tests and no additional hospital visits, we believe it is particularly suitable for broader implementation, including in resource-limited settings, while simultaneously reducing costs associated with emergency episodes and hospital admission in the context of symptomatic VTE. Future studies should focus on determining the prognostic implications of prophylactic anticoagulation in asymptomatic patients, as well as potential drawbacks related to complications such as increased risk of bleeding.

Conclusions

The incidence rate of VTE in lung cancer patients is high and possibly still underestimated. A screening protocol, integrating already established diagnosis and treatment response assessment imaging with inexpensive additional exams conducted at well-accepted reassessment timeframes, proved both feasible and highly effective in identifying embolic events in asymptomatic patients. VTE risk assessment tools can be enhanced by adding D-dimer-based parameters, possibly enabling the periodic re-evaluation of risk throughout treatment.

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Online supplementary material:
Supplementary Table 1. Khorana and COMPASS-CAT risk scores for venous thromboembolism.
Supplementary Table 2. Baseline characteristics of the study population.
Supplementary Table 3. Overview of analytical sampling and imaging results at baseline and 3-month reassessment according to final health status (alive/deceased).
Supplementary Figure 1. Scatterplot of the predicted probability of VTE according to the measured D-dimer serum concentration at baseline (A) and 3-month reassessment (B), relative to the patient's sex.

Table 1. Screening tools (blood analysis and imaging) results at baseline and 3-month reassessment according to confirmation or exclusion of VTE.

	Baseline			**3-month reassessment**		
	Negative screening (n=92)	**Positive screening** (n=10)	*p-value*	**Negative screening** (n=94)	**Positive screening** (n=8)	*p-value*
Blood coagulation tests						
Prothrombin time (sec)	12.5 (10.5-37.4)	13.6 (12.9-15.5)	p<0.001	12.9 (10.8-44.1)	13.9 (11.1-22.6)	0.005
Activated partial thromboplastin time (sec)	32.7 (24.0-50.9)	33.5 (29.0-41.3)	p=0.357	32.1 (23.1-52.9)	30.9 (24.2-42.5)	0.568
Fibrinogen (mg/dL)	438 (241-750)	426 (242-684)	p=0.211	410 (238-753)	390 (363-583)	0.279
D-dimer (mg/L)	1.18 (0.27-9.69)	3.52 (0.89-11.18)	p=0.002	1.32 (0.27-12.30)	5.00 (0.65-13.00)	0.002
Complete blood count						
Hemoglobin (g/dL)	12.9 (8.0-17.6)	11.9 (9.2-15.7)	p=0.397	12.5 (8.5-16.9)	12.4 (9.0-14.5)	0.275
White blood cell count ($x10^9$/L)	8.37 (3.59-22.28)	9.34 (4.24-14.95)	p=0.963	7.93 (3.07-36.93)	8.19 (6.70-36.93)	0.063
Platelet count ($x10^9$/L)	258 (149-533)	297 (182-502)	p=0.508	252 (25-473)	193 (15-448)	0.124
Imaging screening tests						
PE in contrast-enhanced chest CT	0 (0)	2 (20.0)	p<0.001	0 (0)	4 (50.0)	<0.001
DVT in complete duplex ultrasound	0 (0)	8 (80.0)	p<0.001	0 (0)	6 (75.0)	<0.001

CT, computed tomography; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.
Continuous variables presented as median (interquartile range); qualitative variables presented as absolute number (percentage).

Table 2. Interplay between treatment modalities and overall VTE screening results.

	Overall VTE screening		
	Negative (n=86)	**Positive** (n=16)	*p-value*
Curative-intent treatment modalities			
Surgery (VATS)	16 (18.6)	4 (25.0)	0.554
Stereotactic body radiation therapy	17 (19.8)	0 (0)	0.051
Chemoradiation therapy	13 (15.1)	1 (6.2)	0.344
Palliative-intent treatment modalities			
Chemotherapy alone	12 (14.0)	2 (12.5)	0.877
Immune checkpoint inhibitor therapy	24 (27.9)	9 (56.3)	0.026
Immunotherapy alone	16 (18.6)	6 (37.5)	0.092
Chemo-immunotherapy	8 (9.3)	3 (18.8)	0.263
Targeted therapy	4 (4.6)	0 (0)	0.581

VATS, video-assisted thoracoscopic surgery; VTE, venous thromboembolism. Qualitative variables presented as absolute number (percentage).

Table 3. Association between VTE screening positivity and Khorana risk stratification adjusted for significant confounders, including D-dimer serum concentration at baseline (A) and at 3-month reassessment (B) – univariate and multivariate logistic regression analyses.

A	Univariate Analysis		Multivariate Analysis	
	Adjusted HR (95% CI)	*p-value*	Adjusted HR (95% CI)	*p-value*
Sex (male)	**4.80 (1.03-22.47)**	**0.046**	**7.69 (1.22-48.53)**	**0.030**
Age at the time of diagnosis	0.97 (0.91-1.02)	0.214	1.01 (0.94-1.09)	0.724
D-dimer (baseline)	**1.39 (1.14-1.72)**	**0.002**	**1.29 (1.01-1.68)**	**0.050**
Histology (NSCLC vs SCLC)	0.92 (0.18-4.66)	0.921	1.42 (0.19-10.20)	0.730
Staging (metastatic)	3.21 (1.02-10.04)	0.045	2.22 (0.13-39.38)	0.588
First-line treatment (palliative)	2.53 (0.81-7.90)	0.110	0.83 (0.05-15.09)	0.900
Khorana VTE risk class (high)	4.37 (1.38-13.80)	0.012	3.64 (0.79-16.69)	0.096
B	Univariate Analysis		Multivariate Analysis	
	Adjusted HR (95% CI)	*p-value*	Adjusted HR (95% CI)	*p-value*
Sex (male)	**4.80 (1.03-22.47)**	**0.046**	**8.43 (1.04-68.57)**	**0.046**
Age at the time of diagnosis	0.97 (0.91-1.02)	0.214	1.03 (0.95-1.11)	0.516
D-dimer (3-months)	**1.35 (1.16-1.58)**	**<0.001**	**1.33 (1.12-1.59)**	**0.001**
Histology (NSCLC vs SCLC)	0.92 (0.18-4.66)	0.921	0.67 (0.09-4.99)	0.665
Staging (metastatic)	3.21 (1.02-10.04)	0.045	1.66 (0.11-25.02)	0.588
First-line treatment (palliative)	2.53 (0.81-7.90)	0.110	1.32 (0.08-22.30)	0.848
Khorana VTE risk class (high)	**4.37 (1.38-13.80)**	**0.012**	**6.81 (1.32-35.23)**	**0.022**

CI, confidence interval; HR, hazard ratio; NSCLC, Non-small cell lung cancer; SCLC, Small cell lung cancer; VTE, Venous thromboembolism.

Table 4. Association between VTE screening positivity and modified Khorana risk stratification adjusted for significant confounders – univariate and multivariate logistic regression analyses.

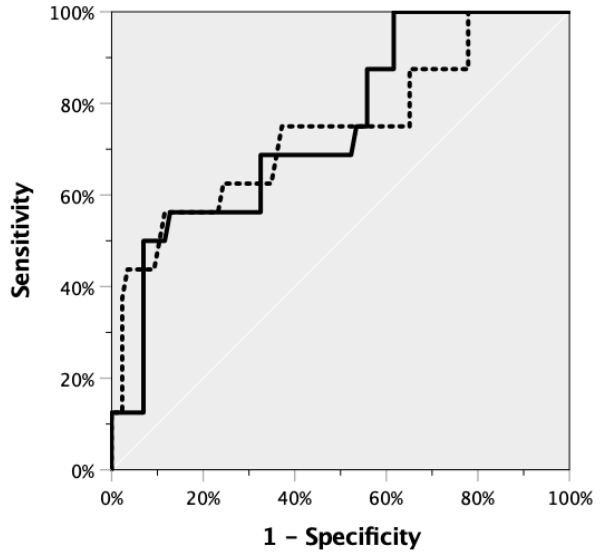
	Univariate Analysis		Multivariate Analysis	
	Adjusted HR (95% CI)	*p-value*	Adjusted HR (95% CI)	*p-value*
Sex (male)	4.80 (1.03-22.47)	0.046	14.84 (0.97-27.98)	0.053
Age at the time of diagnosis	0.97 (0.91-1.02)	0.214	0.96 (0.89-1.03)	0.260
BMI (kg/m^2)	1.39 (1.14-1.72)	0.002	0.89 (0.69-1.14)	0.357
Smoking (active/former smoker)	0.91 (0.26-3.13)	0.880	0.15 (0.07-3.26)	0.224
Cardiovascular comorbidities [a]	1.85 (0.39-8.91)	0.441	25.55 (0.78-83.48)	0.069
COPD	**6.02 (1.59-22.68)**	**0.008**	**4.05 (1.37-24.15)**	**0.009**
Histology (NSCLC vs SCLC)	0.92 (0.18-4.66)	0.921	1.06 (0.10-11.04)	0.961
Staging (metastatic)	3.21 (1.02-10.04)	0.045	1.49 (0.27-8.12)	0.649
mKhorana VTE risk class (high) [b]	**9.77 (2.98-32.04)**	**<0.001**	**16.54 (2.64-103.83)**	**0.003**

BMI, Body-mass index; CI, confidence interval; COPD, Chronic obstructive pulmonary disease; HR, hazard ratio; mKhorana, Modified Khorana; NSCLC, Non-small cell lung cancer; SCLC, Small cell lung cancer; VTE, Venous thromboembolism

[a] Any of the following, alone or in association: arterial hypertension, dyslipidemia, diabetes mellitus, coronary heart disease, periphery arterial disease, chronic kidney disease.

[b] mKhorana risk class – upscaled from baseline Khorana score if D-dimer serum concentration 4.50 mg/L at 3-month reassessment (+2 points).

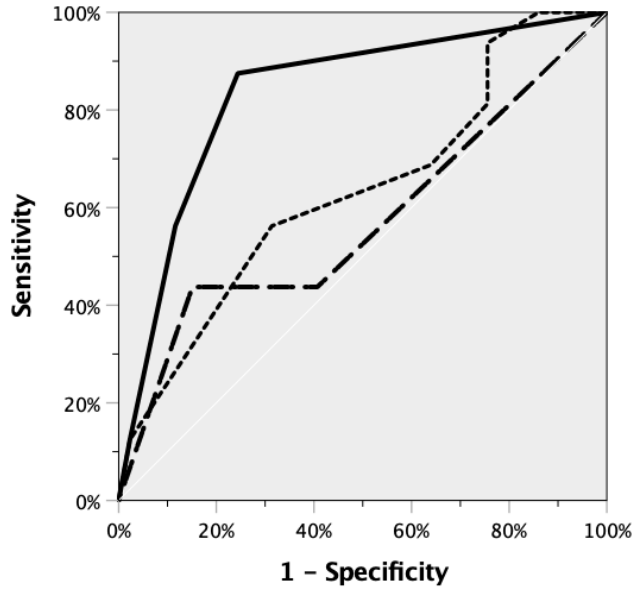
A



Baseline

3-month reassessment

B



mKhorana

Khorana

COMPASS-CAT

Figure 1. ROC curve analysis comparing the diagnostic accuracy of D-dimer serum concentration at baseline and 3-month reassessment [AUC=0.746 (95%CI 0.618-0.873) at baseline and AUC=0.741 (95%CI 0.593-0.888) at 3-months; p=0.002] (A) and the predictive capacity of different risk stratification scores [AUC=0.834 (95%CI 0.725-0.943) for mKhorana; p<0.001] (B) for VTE screening positivity.