Received: 17 July 2023 | Revised: 18 January 2024 | Accepted: 9 February 2024

https://doi.org/10.1016/j.rpth.2024.102359

ORIGINAL ARTICLE

Plasma tissue factor activity in lung cancer patients predicts venous thromboembolism and poor overall survival

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Handling Editor: Dr Henri Spronk.

Abstract

Background: Biomarkers to identify lung cancer (LC) patients with high risk of venous thromboembolism (VTE) are needed.

Objectives: To evaluate the usefulness of plasma tissue factor activity (TFA) and D-dimer levels for the prediction of VTE and overall survival in patients with LC.

Methods: In a prospective multicenter observational cohort of consecutive LC patients, TFA and D-dimer levels were measured at diagnosis before any cancer treatment (V1) and between 8 and 12 weeks after diagnosis (V2).

Results: Among 302 patients, 38 (12.6%) experienced VTE within the first year after diagnosis. V1-TFA and V1-D-dimer levels were significantly (P = .02) higher in patients who presented VTE within 3 months than in patients without VTE: V1-TFA was 2.02 (25th-75th percentiles, 0.20-4.01) vs 0.49 (0.20-3.09) ng/mL and V1-D-dimer was 1.42 (0.64-4.40) vs 0.69 (0.39-1.53) μg/mL, respectively. Cutoffs of 1.92 ng/mL for TFA and 1.26 μg/mL for D-dimer could discriminate both groups of patients. In multivariate analysis, V1-TFA > 1.92 ng/mL was the only significant predictor of VTE risk at 1 year (hazard ratio, 2.10; 95% CI, 1.06-4.16; P = .03). V2-TFA, quantified in 251 patients, decreased significantly compared with V1-TFA (0.20 vs 0.56 ng/mL, P < .05), but a V2-TFA level > 0.77 ng/mL could predict VTE in the following 3 months. Median overall survival was worse for patients with V1-TFA > 1.92 ng/mL (14.6 vs 23.8 months) and V1-D-dimer > 1.26 μg/mL (13.8 vs 24 months, P < .001).

Conclusion: High plasma TFA levels are associated with the occurrence of VTE within the next 3 months after each visit (V1 or V2) and poor survival.

KEYWORDS
D-dimer, lung neoplasms, survival, thromboplastin, venous thromboembolism

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Essentials

- Incidence of venous thromboembolism (VTE) is high in lung cancer.
- We aimed to select patients with a high risk of VTE using tissue factor activity (TFA) and D-dimer.
- High plasma TFA and D-dimer levels in patients with lung cancer predict the occurrence of VTE in the next 3 months after each visit (V1 or V2).
- Median overall survival is worse in patients with high levels of TFA and D-dimer.

1 | INTRODUCTION

Among solid tumors, lung cancer (LC) has one of the highest incidences of venous thrombotic events, reaching up to 15% [1]. The risk of venous thromboembolism (VTE) varies throughout the course of cancer disease, preceding the diagnosis of cancer or occurring mainly in the first months of treatment [2]. Identifying patients with high risk of VTE and strategies to avoid these cancer-associated thromboses (CAT) is still a central and unresolved question.

Various predictive scores have been evaluated to select patients at higher risk of CAT. Among them, the Khorana score (KS), based on clinical and hematologic parameters, is one of the most recognized [3]. Recently published trials have evaluated thromboprophylaxis with direct oral anticoagulants in cancer patients with a KS of 2 or more at the initiation of systemic treatment, and different guidelines recommend considering prophylactic anticoagulation in such patients [4–6]. However, in many studies, KS failed to predict VTE in LC patients [7–11], and clinicians remain hesitant to propose treatments with potential bleeding complications [4,12]. Therefore, other approaches to identify LC patients with a high risk of VTE are clearly needed. Interestingly, interplay between hemostatic system and tumor cells goes beyond thromboembolic complications and also impacts tumor biology (tumor growth, disease progression, and metastatic spread) with possible consequences on survival of the patients [13,14].

In addition to the KS, various prothrombotic biomarkers (D-dimer, P-selectin, prothrombin fragment 1 + 2, and factor VIII) have been evaluated for their predictive value for CAT, response to anticancer treatment, and overall survival (OS) [15,16]. D-dimer, a fibrin degradation product, is one of the most studied parameters. In large prospective cohort studies, a high level of D-dimer in patients with different types of cancer before any antitumor treatment was shown to be associated with an increased risk of VTE and poorer OS [17,18].

Tissue factor (TF) is a transmembrane receptor that binds FVII and is considered the main physiologic initiator of the coagulation cascade *in vivo* [19]. Under physiological conditions, TF, expressed by adventitial cells surrounding blood vessels, initiates coagulation in case of vascular injury [20]. Under pathological conditions, TF can be present on the surface of tumor and possibly on vascular endothelial cells supplying the tumor and triggers both arterial and venous thrombosis [21,22]. In addition, the intracellular domain of TF can promote tumor growth either directly by stimulating oncogenes like RAS or indirectly by activating protease-activated receptor-2 by the TF/activated FVII complex, which leads to angiogenesis and metastasis [23,24]. Two forms of TF have been described in plasma. Full-length TF, released by activated cells [25], circulates associated with extracellular vesicles (EVs) and, if not encrypted [26], has a potent procoagulant activity. Alternatively, spliced TF has little to no procoagulant activity but plays a role in neoangiogenesis and cancer progression by interactions with integrins [27].

The predictive value of tumor TF expression or its plasma level on VTE occurrence and prognosis in LC patients is controversial [28–34], possibly because of the method used to detect TF. Some studies evaluated the presence of TF (protein or RNA levels) in tumor tissues [28,29], and others assessed the presence of TF-exposing EVs in blood by flow cytometry or immunocapture, but the specificity of the antibody against TF was sometimes questionable [35]. Furthermore, antigenic determination of TF is not predictive of its activity, and it has been shown that LC chemotherapy could increase its procoagulant activity via protein disulfide isomerase-dependent TF decryption [36]. Lastly, there are few prospective studies evaluating TF in LC [28–29,31–33,37].

Therefore, using an assay that quantified plasma TF activity (TFA), we conducted a prospective multicenter trial to determine whether plasma TFA and D-dimer at diagnosis could be useful to predict VTE risk as well as tumor control rate and OS in ambulatory LC patients. In addition, these markers were also quantified between 8 and 12 weeks after diagnosis when a first tumor evaluation was performed.

2 | METHODS

2.1 | Patients

Patients aged over 18 years with a histologic diagnosis of non–small cell lung cancer (NSCLC) or small cell lung cancer (SCLC) and a life expectancy estimated to be superior to 3 months were included consecutively in 5 French hospitals before any cancer treatment.

Exclusion criteria were hepatic disease with coagulation disorders, therapeutic anticoagulation in the preceding 3 months, active infection, or other active cancer within the last 5 years. Antiplatelet therapy was allowed.

Demographic characteristics, history of VTE, smoking status, Eastern Cooperative Oncology Group (ECOG) *performance status*, and body mass index (BMI) were recorded at inclusion. Histologic and stage classification was done according to the tumor node metastasis classification of malignant tumors 7th edition [38].

Anticancer treatments received during the first 3 months were collected, and KS was evaluated. According to the Response Evaluation Criteria in Solid Tumors (version 1.1) [39], physicians assessed at first evaluation (8-12 weeks after initiation) whether the tumor was progressive or controlled (as disease control represents complete response, partial response, and stable disease).

Patients were followed up for 2 years for the occurrence of symptomatic or incidental VTE and survival. In this noninterventional study, imaging tests (Doppler ultrasound, computed tomography, or ventilation/perfusion lung scans) were performed following local practice in case of VTE symptoms or usual lung cancer management.

The study was performed in accordance with the Helsinki Declaration and Good Clinical Practice guidelines and was approved by the Independent Ethics Committee Ile de France. Written informed consent was obtained for each patient before enrollment and blood sampling. The trial is registered with ClinicalTrial.gov, number NCT02853188.

2.2 | Blood sampling and assays

Blood samples were collected before any cancer treatment (V1) and between 8 and 12 weeks after initiation of treatment (V2). D-dimer and TFA measurements were performed in a central laboratory while the other coagulation parameters (prothrombin time, activated partial thromboplastin time, and fibrinogen) and the complete blood count with differential were analyzed in the biology department of each center.

For coagulation assays, blood was collected into citrated tubes (Sarstedt) containing 3.2% trisodium citrate as anticoagulant in a ratio of 9 parts of blood to 1 part of citrate. Platelet-poor plasma was prepared by double centrifugation for 20 minutes at 2000 × g at room temperature. Samples were tested immediately or quickly frozen at −80 °C for future assays. D-dimer levels (D-dimer HS 500, Werfen) were measured using an ACL 700 analyzer (Werfen). TFA was measured by a one-stage kinetic chromogenic method, which measures the ability of TF-activated FVII (FVIIa) complex to activate FX [40]. Citrated plasma was diluted 1:3 in Owren-Koller buffer containing a neutralizing antibody against the TF Pathway Inhibitor (T4E2, Diagnostica Stago) at a final concentration of 10 μg/L and an inhibitor of fibrinoformation (final concentration 2 g/L) (Pefabloc FG, Pentapharm). To 50 μL of diluted plasma, 25 μL of FX (Enzyme Research Laboratories Ltd) adjusted to 80 Plasma Equivalent Units/mL (PEU/mL), 25 μL of FVII (Enzyme Research Laboratories Ltd) adjusted to 137 PEU/mL, and 50 μL of calcium chloride (25 mM) were added and incubated at 37 °C for 500 seconds. The amidolytic activity of the TF-FVIIa complex formed was quantified by measuring the amount of activated FX (FXa) produced using the FXa substrate CBS 52.44 (Diagnostica Stago). Absorbance at 405 nm was monitored between 6 and 600 seconds on STA analyzer (Diagnostica Stago). For patients treated with heparin at V2, heparin activity was blocked by polybrene, and hirudin was added to the dilution buffer at final concentrations of 2.5 mg/mL and 5 U/mL, respectively. Calibration was performed using STA-Neoplastine R (Diagnostica Stago) as a calibrator. Interferences of hemoglobin, bilirubin, and lipids were studied on plasmas artificially overloaded with TF. Hemoglobin up to 0.2 g/dL, bilirubin up to 30 mg/dL, and lipids up to 1000 mg/dL did not interfere with TFA measurement. The monoclonal antibody 5G9 (Interchim), previously described as an efficient inhibitor of TFA in plasma [41], inhibited 97% of the TFA in a plasma overloaded with 1.2 ng/mL of TF. TFA median value was 0.19 ng/mL [25th percentile, 0.16; 75th percentile, 0.21] in 83 healthy volunteers.

2.3 | Statistical analysis

Descriptive analyses were performed with median and 25th and 75th percentiles (indicated in square brackets) for continuous variables and numbers and frequencies for categorical variables. Patients who presented VTE were compared to patients without VTE using Mann–Whitney U-test for continuous variables and chi-squared or Fisher's exact tests for categorical variables. Spearman test was used for correlation analysis between TFA and D-dimer.

To predict the VTE occurrence with baseline levels of D-dimer and TFA, a receiver operating characteristic (ROC) curve model was used to determine the best cutoff necessary to discriminate a population with VTE using the area under the curve (AUC) and the Youden index. Sensitivity and specificity were calculated for different time occurrences of VTE (3 months, 6 months, and 1 year), and repartition of each biomarker cutoff was compared with a Fisher's exact test.

The impacts of D-dimer and TFA cutoffs on the risk of VTE after 1 year were evaluated through univariate Cox proportional hazards models. A multivariate model was then performed, including both cutoffs and adjusted for individual characteristics significant at level 0.20 in univariate analysis (among KS, sex, smoking history, chemotherapy, BMI, NSCLC, and stage IV disease). A "backward" selection model was used to achieve the best interpretable adjusted model.

A univariate Cox model was used to evaluate the association between OS and D-dimer cutoff and TFA cutoff. A multivariate model was then performed, including both cutoffs and adjusted for significant individual characteristics at level .20 in univariate analysis (among age, KS, sex, stage IV disease, disease control, and VTE). A "backward" selection model was used to achieve the best interpretable adjusted model.

OS was estimated using the Kaplan–Meier estimator, and groups were compared using log-rank tests for both biomarkers.

All analyses were 2-tailed, and $P < .05$ was considered statistically significant unless specified otherwise. Analyses were conducted using SAS 9.4 (SAS Institute).

3 | RESULTS

3.1 | Patients

From December 2014 to January 2017, 317 patients were recruited. Fifteen patients were not eligible (11 cases because of the history of a

TABLE 1 Baseline characteristics of the 302 patients and their tumors.

Characteristic	*n* (%)
Median age [25th-75th percentile], y	64 [58-71]
Sex	
Female	119 (39.4)
Male	183 (60.6)
Ethnicity	Not recorded[a]
Smoking history	
Current smoker	110 (36.4)
Former smoker	159 (52.6)
Never smoker	33 (11)
Performance status	
0	176 (59.1)
1	103 (34.5)
2	19 (6.4)
Comorbidities	
Hypertension	109 (36.1)
Heart disease	53 (17.5)
Chronic obstruction pulmonary disease	49 (16.2)
Renal failure	5 (1.7)
Body mass index > 35 kg/m^2	5 (1.7)
Previous thromboembolic events	
Arterial stroke/myocardial infarction	11/11 (3.6/3.6)
Pulmonary embolism/deep venous thrombosis	1/5 (0.3/1.7)
Tumor histology	
Small cell lung cancer and composite	46 (15.2)
Nonsmall cell lung cancer	256 (84.8)
Adenocarcinoma	*171*
Squamous cell carcinoma	*53*
Other tumors	*32*
Tumor stage	
I	4 (1.3)
II	27 (8.9)
III	63 (20.9)
IV	186 (61.6)
Not indicated	22 (7.3)
Treatment within the first 3 mo	
Chemotherapy[b]	266 (88.1)
Alone	179
With radiotherapy	*69*
With surgery	*18*
Radiotherapy only	4 (1.3)
Surgery only	14 (4.6)
Not indicated	18 (6.0)
Tumor assessment 8-12 weeks after treatment initiation	
Disease control	241 (79.8)
Progression disease	61 (20.2)
Khorana score	
≥2	172 (56.9)/137 (51.5)[c]
≥3	63 (20.9)/58 (21.8)[c]

[a]In accordance with French legislation.
[b]Platin-based chemotherapy was used in 239/266 (89.8%).
[c]When considering only patients treated with chemotherapy.

second active cancer). The characteristics of the 302 included patients are shown in Table 1; median age was 64 [58-71] years, 60.6% was male, 89% were smokers or former smokers, and 19 (6.3%) had a *performance status* ≥2. The main histology was NSCLC (256 patients, 84.8%); 186 (61.6%) had stage IV disease.

Previous arterial thromboembolic events (ischemic stroke or myocardial infarction) were noted in 22 (7.3%) patients, whereas 6 (2%) had VTE in their past history.

The main systemic first-line treatment was chemotherapy (266 patients, 88.1%) alone (179/266, 67.3%) or associated with surgery (18/266, 6.8%) or radiotherapy (69/266, 25.9%). Surgery was performed only in 14 (4.6%) patients, and radiotherapy in 4 (1.3%) patients. Tumor disease was controlled in 241 (79.8%) patients.

KS was ≥2 in 172 (56.9%) of the 302 patients and ≥3 in 63 (20.9%) patients.

3.2 | Venous thromboembolism events

Thirty-eight patients (12.6%) developed VTE during the first year of follow-up: 23 (60.5%) within the first 3 months, 10 (26.3%) between the third and sixth months, and 5 (13.2%) after 6 months (Table 2). Twenty-three events (60.5%) were detected incidentally. Only 3 of the 38 events happened in SCLC. Pulmonary embolism, with or without deep vein thrombosis, occurred in 22 patients (57.9%); 16 (42.1%) had isolated deep vein thrombosis. Recurrent events of VTE occurred in 4/38 (10.5%) patients. The median duration between inclusion and VTE occurrence was 2.3 months [1.6-5.8].

KS at diagnosis was ≥2 in 65.8% and ≥3 in 21% of the 38 patients who had VTE.

Most patients with VTE (94.6%) were treated with low-molecular-weight heparin.

TABLE 2 Characteristics of the 38 thromboembolic events within the first year after diagnosis.

Characteristic	*n* (%)
Total events	38
Type of event	
Pulmonary embolism	20 (52.6)
Deep vein thrombosis	16 (42.1)
Both	2 (5.3)
Incidental events	23 (60.5)
Time of occurrence (after inclusion)	
0-3 mo	23 (60.5)
3-6 mo	10 (26.3)
6-12 mo	5 (13.2)
Tumors	
Nonsmall cell lung cancer	35 (92.1)
Stage IV disease	24 (63.1)
Treatment within the first 3 mo	
Chemotherapy only	17 (44.7)
Chemotherapy + surgery	2 (5.3)[a]
Chemotherapy + radiotherapy	15 (39.5)
Radiotherapy only	2 (5.3)
Not indicated	2 (5.3)
Khorana score at inclusion ≥2	25 (65.8)/23 (67.6)[b]
Khorana score at inclusion ≥3	8 (21)/8 (23.5)[b]

[a]No thromboembolic event was observed within 30 days after surgery.
[b]When considering only patients treated with chemotherapy.

3.3 | Baseline levels of D-dimer and *TFA* and risk of *VTE*

At inclusion (V1), median TFA and D-dimer levels were 0.77 (0.2-3.1) ng/mL and 0.71 (0.40-1.65) μg/mL, respectively. Median levels of both biomarkers were not different between NSCLC and SCLC patients. D-dimer but not TFA levels increased significantly (P = .004) with stage (Supplementary Tables S1 and S2).

Using a Spearman test, we did not find any relevant correlation between TFA and D-dimer, neither in the entire cohort since the correlation coefficient was 0.28 (95% CI, 0.17; 0.38), nor in the NSCLC group for which the correlation coefficient was 0.15 (95%CI, −0.17; 0.44).

Baseline TFA and D-dimer were not significantly different in the 38 patients who experienced VTE within 1 year from those who did not. However, when the analysis was restricted to the 23 patients who experienced VTE within the first 3 months, median levels of both biomarkers were significantly higher in VTE patients than in no VTE patients: 2.02 [0.2-4.01] vs 0.49 [0.2-3.09] ng/mL (P = .02), and 1.42 [0.64-4.40] vs 0.69 [0.39-1.53] μg/mL (P = .02) for TFA and D-dimer, respectively (Table 3). As SCLC patients and NSCLC have different clinical patterns, we investigated whether their exclusion modified the conclusions of the study (even if SCLC represented a minority subset of the cohort). TFA and D-dimer levels had the same levels and distribution in the NSCLC cohort and in the entire cohort for the patients who had VTE at 3, 6, and 12 months, but the differences between patients with and without thrombosis were not statistically significant in the NSCLC cohort.

Using ROC curve analysis, cutoffs of 1.92 ng/mL for TFA and 1.26 μg/mL for D-dimer were predictive of VTE within the first 3 months after cancer diagnosis with sensitivity and specificity of 61% and 68%, and 68% and 71%, respectively.

As international guidelines recommend to discuss or consider thromboprophylaxis for patients with a KS of 2 or more [42], we evaluated the performance of these 2 biomarkers to identify patients who will experience VTE and compared them with KS (Supplementary Table S3). The proportion of patients who developed VTE within the first 3 months was 13.9% in patients with TFA > 1.92 ng/mL and 13% in patients with D-dimer > 1.26 μg/mL, whereas it was 8.7% in patients with KS ≥ 2. Among patients with VTE within the first 3 months, 60.9% and 60% had TFA or D-dimer levels higher than the cutoffs, respectively, whereas 65% had a KS ≥ 2. Nevertheless, the specificities of these biomarkers were higher (68% for TFA and 69% for D-dimer) than that of KS (43%). As a KS ≥ 3 defines patients with a high risk of VTE, we also compared its performance to TFA and D-dimer. The specificity of KS ≥ 3 was higher (79.2%) than the specificities of TFA and D-dimer, but the sensitivity was very low (21.7%). The negative predictive value was 95% for TFA and D-dimer and 93% for KS (≥2 or ≥3).

In univariate analysis, a threshold of 1.92 ng/mL for TFA and a cutoff >1.26 μg/mL for D-dimer were significantly associated with a higher risk of VTE at 1 year (Table 4). Other parameters like sex, smoking history, BMI > 35 kg/m^2, disease stage, histology, chemotherapy, and KS ≥ 2 were not associated with VTE at 1 year. In multivariate analysis, TFA > 1.92 ng/mL was the only significant factor for 1-year VTE risk (hazard ratio [HR], 2.10; 95% CI, 1.06-4.16; P = .03).

3.4 | Baseline levels of D-dimer and tissue factor activity and overall survival

After a median follow-up of 24.9 months, median OS was 19.2 months, with survival rates of 95%, 87.1%, 67.9%, and 45% at 3 months, 6 months, 1 year, and 2 years, respectively. Deaths were related to VTE in 1 case and to cancer progression in all other cases. Median OS in patients with and without VTE were 17.4 and 19.7 months, respectively (P = .81). There was a significantly worse OS for patients with TFA > 1.92 ng/mL compared with others (14.6 vs 23.8 months, P < .001), and for patients with D-dimer > 1.26 μg/mL compared with others (13.8 vs 24 months, P < .001) (Figure 1).

TABLE 3 Tissue factor activity and D-dimer levels at diagnosis according to time of occurrence of venous thromboembolism.

Time after inclusion	Biomarker	With VTE	Without VTE	*P*
<3 mo	*n*	23	278	
	TFA (ng/mL)	2.02 [0.20-4.01]	0.49 [0.20-3.09]	.02
	D-dimer (μg/mL)	1.42 [0.64-4.40]	0.69 [0.39-1.53]	.02
<6 mo	*n*	33	268	
	TFA (ng/mL)	1.90 [0.20-3.10]	0.50 [0.20-3.10]	.08
	D-dimer (μg/mL)	1.10 [0.30-2.80]	0.70 [0.40-1.60]	.44
<12 mo	*n*	38	264	
	TFA (ng/mL)	1.78 [0.20-3.15]	0.46 [0.20-3.15]	.07
	D-dimer (μg/mL)	0.86 [0.32-2.54]	0.70 [0.42-1.57]	.69

Values are expressed as median [25th-75th percentiles].
TFA, tissue factor activity; VTE, venous thromboembolism.

In univariate analysis, factors significantly associated with a poor OS were D-dimer levels ≥ 1.26 μg/mL (HR, 1.89; 95% CI, 1.38-2.60; $P < .001$), TFA ≥ 1.92 ng/mL (HR, 1.66; 95% CI, 1.22-2.27; $P = .001$), stage IV disease (HR, 2.64; 95% CI, 1.80-3.88; $P < .001$), KS ≥ 2 (HR, 1.47; 95% CI, 1.08-2.01; $P = .015$), age (HR, 1.02; 95% CI, 1.00-1.03; $P = .018$), and male sex (HR, 1.75; 95% CI, 1.25-2.44; $P = .001$), whereas disease control was associated with best OS (HR, 0.34; 95% CI, 0.23-0.50; $P < .001$).

In multivariate analysis, adjusted for age, stage IV disease, and disease control, only TFA ≥ 1.92 ng/mL remained significantly associated with worse OS (HR, 1.52; 95% CI, 1.06-2.17; $P = .02$), whereas D-dimer did not (Table 5).

3.5 | Dynamic changes of D-dimer and tissue factor activity between diagnosis (V1) and first tumor evaluation (V2)

TFA and D-dimer could be analyzed in 251 patients at V2 (V2-TFA and V2-D-dimer) (Table 6). Nine patients died before V2. Compared with V1, V2-TFA significantly decreased (0.20 vs 0.56 ng/mL, $P < .05$), whereas V2-D-dimer was not significantly different (0.90 vs 0.70 μg/mL, $P = .17$). Nevertheless, V2-TFA levels were increased in some groups of patients:

a) patients who had VTE before V2 (7.46 [3.15-13.50] ng/mL) and those who had VTE within the next 3 months after V2 (1.85 [0.9-

TABLE 4 Univariate and multivariate Cox proportional hazards model for the risk of venous thromboembolism at 1 year. The multivariate model is a backward selection model including tissue factor activity and D-dimer, adjusted for Khorana score ≥ 2. The final model is reported.

	Univariate analysis			Multivariate analysis (*N* = 279)		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
TFA ≥ 1.92 ng/mL	2.16	1.14-4.08	.018	2.10	1.06-4.16	.034
D-dimer ≥ 1.26 μg/mL	2.06	1.05-4.03	.036	1.81	0.91-3.59	.089
Khorana score ≥ 2	1.59	0.81-3.11	.176			
Sex (male)	0.92	0.48-1.75	.79			
Smoking history			.32			
Smoker	1	-				
Former smoker	1.27	0.61-2.64				
Nonsmoker	2.08	0.80-5.34				
Chemotherapy	1.05	0.37-2.97	.92			
BMI > 35 kg/m^2	1.54	0.21-11.20	.67			
NSCLC	2.04	0.63-6.64	.236			
Stage IV	1.26	0.62-2.56	.52			

BMI, body mass index; HR, hazard ratio; NSCLC, nonsmall cell lung cancer; TFA, tissue factor activity.

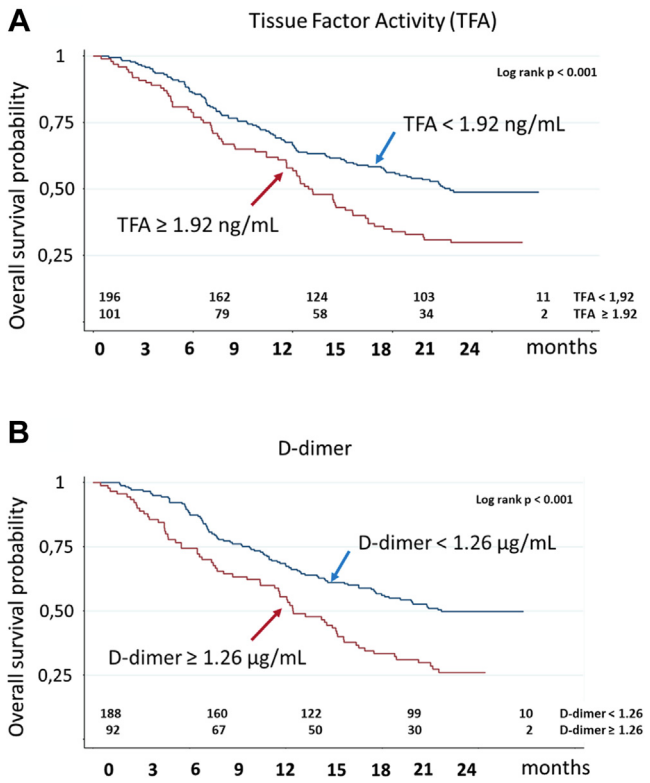

FIGURE 1 Kaplan–Meier curve analysis of the overall survival for the total cohort dichotomized by each biomarker level at diagnosis according to (A) the level of tissue factor activity (TFA) or (B) the level of D-dimer (for the 302 patients). The difference between groups was determined by the log-rank test.

4.4.4] ng/mL). Using ROC curve analysis, we observed that a level of V2-TFA > 0.77 ng/mL could discriminate patients who will experience VTE within the next 3 months after V2 from patients who will have a thrombotic event later or no thrombotic event (sensitivity = 85.7%; specificity = 71.1%; AUC = 0.771);

b) patients who presented disease progression (1.54 [0.20-5.94] ng/mL); and

c) patients who died between V2 and 6 months after diagnosis (1.10 [0.20-7.59] ng/mL), but the difference was not significant (P = .06).

In contrast, D-dimer levels increased significantly (P < .01) between V1 and V2 in patients with tumor progression. Moreover, in patients who died before the 6th month after diagnosis, V2-D-dimer levels were significantly higher (P < .01) than in patients who died later or survived during follow-up. A ROC curve analysis indicated that a cutoff of 1.64 µg/mL of V2-D-dimer could discriminate patients at high risk of dying before 6 months after diagnosis (sensitivity and specificity were 55.9% and 78.8%, respectively; AUC = 0.697).

4 | DISCUSSION

This large prospective multicenter trial sought to evaluate the predictive value of coagulation biomarkers on VTE risk within the first year after diagnosis in ambulatory LC patients. The characteristics of our population are comparable to those of other cohorts with LC: the majority were men and smokers or former smokers, more than 80% had NSCLC, 61.6% had metastatic disease, and 88.1% were treated by chemotherapy. Incidence of VTE at 1 year (12.5%) was in the range of other recent cohorts in LC; more than 50% of the thrombotic events happened within the first 3 months of diagnosis, as commonly reported in LC patients populations [12,43]. Baseline TFA and D-dimer continuous levels were higher in patients who experienced VTE than in those who did not, but the difference was significant only for the earliest events within the first 3 months. Therefore, we proposed a cutoff of 1.92 ng/mL of V1-TFA and 1.26 µg/mL for V1-D-dimer to identify patients with a high risk of early VTE. Nevertheless, in multivariate analysis, this threshold (TFA > 1.92 ng/mL at diagnosis) was associated with a 2.10-fold increase in the HR for 1-year VTE risk. At this time, to our knowledge, the assay we used in this study was not tested in other studies related to the thrombotic risk of cancer patients. However, D-dimer levels were extensively studied, and the cutoff determined to identify patients with an increased thrombotic risk was similar to ours: 1.44 µg/mL in the Cancer and Thrombosis Study (with less than 15% of LC) [17] and 1.5 µg/mL in a prospective study including 129 patients with NSCLC [43].

We also compared whether TFA and D-dimer at diagnosis were more efficient than KS in discriminating patients with a risk of VTE. Both baseline TFA and D-dimer were significantly more specific and had a better positive predictive value than KS ≥ 2, without difference in terms of sensitivity. Consequently, the use of these biomarkers could have a greater potency to select patients for preventive anticoagulant therapy than the selection of patients by the KS, which is not so effective in LC, as shown once again in a large prospective cohort [44].

TABLE 5 Univariate and multivariate Cox proportional hazards model for overall survival. The multivariate model is a backward selection model including tissue factor activity and D-dimer, adjusted for sex, age, stage IV, Khorana score, and disease control. The final model is reported.

	Univariate analysis			Multivariate analysis (N = 245)		
Variable	HR	95% CI	P	HR	95% CI	P
TFA ≥ 1.92 (ng/mL)	1.66	1.22-2.27	.001	1.52	1.06-2.17	.02
D-dimer ≥ 1.26 (µg/mL)	1.89	1.38-2.60	<.001	1.35	0.94-1.93	.10
Stage IV	2.64	1.80-3.88	<.001	2.65	1.71-4.12	<.001
Disease control	0.34	0.23-0.50	<.001	0.33	0.22-0.51	<.001
Age (per year)	1.02	1.00-1.03	.018	1.02	1.00-1.04	.016
Sex (male)	1.75	1.25-2.44	.001			
Khorana score ≥ 2	1.47	1.08-2.01	.015			
VTE	1.05	0.67-1.64	.834			

HR, hazard ratio; TFA, tissue factor activity; VTE, venous thromboembolism.

TABLE 6 Dynamic evaluation of tissue factor activity and D-dimer at visits 1 and 2 (8-12 weeks after cancer treatment initiation).

	TFA (ng/mL), median [25th-75th percentiles]		D-dimer (µg/mL), median [25th-75th percentiles]	
Patients	**V1**	**V2**	**V1**	**V2**
All patients (*N* = 251)	0.56 [0.20-3.13]	0.20[a] [0.20-1.92]	0.70 [0.38-1.60]	0.90 [0.49-1.69]
VTE				
Without VTE (*n* = 218)	0.45 [0.20-3.15]	0.20 [0.20-1.13]	0.70 [0.39-1.57]	0.92 [0.51-1.74]
With VTE before V2 (*n* = 19)	1.50 [0.20-3.00]	7.46 [3.15-13.50]	1.18 [0.45-3.02]	0.68 [0.41-0.93]
With VTE up to 90 days after V2 (*n* = 7)	1.62 [0.71-2.72]	1.85[d] [0.90-4.40]	0.34 [0.27-1.03]	0.66 [0.49-1.11]
With VTE more than 90 days after V2 (*n* = 7)	0.20 [0.20-3.02]	0.20 [0.20-0. 20]	0.35 [0.30-1.31]	0.55 [0.46-1.74]
Evolution of the tumor				
Disease control (*n* = 207)	0.62 [0.20-3.15]	0.20[c] [0.20-1.40]	0.68 [0.38-1.60]	0.82 [0.45-1.40]
Disease progression (*n* = 39)	1.04 [0.20-4.00]	1.54[a] [0.20-5.94]	0.92 [0.41-1.58]	1.79[b,e] [0.80-2.50]
Survival				
Survivors (*n* = 112)	0.20 [0.20-1.94]	0.20 [0.20-0.91]	0.55 [0.32-1.05]	0.73 [0.41-1.22]
Death before V2 (*n* = 9)	8.34 [1.00-14.70]	N.A	3.51 [1.10-5.80]	N.A
Death between V2 and less than 6 mo after diagnosis (*n* = 34)	1.76 [0.20-5.01]	1.10 [0.20-7.59]	1.42 [0.61-2.50]	1.83[f] [0.83-3.07]
Death more than 6 mo after diagnosis (*n* = 105)	1.04 1. [0.20-3.91]	0.20[a] [0.20-0.91]	0.71 [0.46-1.67]	0.94 [0.59-1.68]

N.A, not available; TFA, tissue factor activity; V1, visit 1; V2, visit 2 (8-12 weeks after cancer treatment initiation); VTE, venous thromboembolism.
[a]$P < .05$.
[b]$P < .01$ vs V1.
[c]$P < .001$ V2 vs V1.
[d]$P < .05$ VTE up to 90 days after V2 vs VTE more than 90 days after V2.
[e]$P < .001$ between disease control and disease progression;
[f]$P < .01$: comparison between death between V2 and less than 6 months after diagnosis and death more than 6 months after diagnosis.

We hypothesized that these biomarkers could be useful to predict VTE during the first year after the diagnosis, but they were predictive of the thrombotic risk only for the first 3 months after the diagnosis. In fact, it is not really that surprising since coagulation is a dynamic and adaptive process, and it can be hypothesized that VTE occurring early after cancer diagnosis is not directly related to the liberation of TF by tumor cells but could be related, for example, to endothelial cell activation by chemotherapy [45]. However, it is interesting to note that in patients whose tumor was controlled, TFA decreased significantly between V1 and V2 and was very often undetectable, whereas, in patients with a progression of the disease, TFA remained elevated, suggesting that TFA is related in part to tumor aggressiveness.

Although VTE occurred almost 1 month before the blood sample, an elevated level of V2-TFA can be noted in the 19 patients who presented VTE before V2 (and received low-molecular-weight heparin), suggesting that TF contributed to the onset of the thrombotic process. Even if the analysis only covers 14 measurements, V2-TFA levels were significantly higher in patients who presented VTE in the next 3 months than those who had VTE later or did not have VTE, and a level of V2-TFA > 0.77 ng/mL seems to identify patients with a persistent high thrombotic risk. This observation strengthens the hypothesis that high TFA levels can select patients with high risk of VTE within the next 3 months after V2 but not for longer time. In contrast, V2-D-dimer levels were not associated with a future VTE.

OS was significantly worse in patients with high levels of TFA or D-dimer at diagnosis. Several studies described an association between high D-dimer levels and poor prognosis in lung cancer patients [46–48]. However, it has been suggested that disease stage could interfere with this association [18,48,49]. In contrast, we did not detect any correlation between TFA and disease stage. This could perhaps explain why, in our series, which included patients at different stages of cancer, only high baseline levels of TFA were identified as an independent predictor of increased mortality in multivariate analysis. Plasma levels of TF associated with EVs (EV-TF) and EV-TF activity have been previously shown to be related to the prognosis of cancer, particularly in pancreatic cancer [37,50], but to our knowledge, this is the first study to report an association between plasma TFA levels and OS in LC. During the follow-up, we did not find a relationship between TFA levels at V2 and OS, in agreement with the study of Gezelius et al. [32], who studied TF antigen and EV-TF activity after treatment of SCLC. In survivors and patients who died more than 6 months after diagnosis, we did not detect significant variations of V2-TFA. In contrast, a high level of V2-D-dimer (>1.64 µg/mL) was associated with early death (<6 months after diagnosis). Our results are slightly

different from those of Ge et al. [51], who observed that patients with persistent positivity of D-dimer after chemotherapy had a shorter progression-free survival [51].

We acknowledge some limitations in our study. The population was heterogeneous in terms of histology, stage of tumors, and treatments. The sample size and the number of VTEs were quite scarce to explore differences between subgroups of patients and evaluate capacity of TFA and D-dimer to predict recurrent VTE. Among the 46 patients with SCLC or composite cancers, 3 (6.5%) presented VTE in the year following diagnosis vs 35 (13.7%) of the 256 patients with NSCLC. VTE rates were not significantly different in the 2 groups (P = .266). When excluding patients with SCLC, despite similar values and distribution in the NSCLC cohort compared with the entire cohort analyzed, we did not find significant results in the NSCLC cohort, which can be explained by a smaller number of patients. Similarly, the cutoffs determined in the entire cohort for the prediction of the VTE risk could not provide predictive performance in the NSCLC group, again probably because of the small number of patients in this group. Nevertheless, in the NSCLC group, we noticed that a high level of TFA (>1.92 ng/mL) and D-dimer >1.26 μg/mL were significant prognostic factors in multivariate analysis. We recorded a high proportion of incidental events, and VTE was not adjudicated by an independent committee. These points could have had an impact on the results of the study. Patients' ethnicity was not recorded, but to our knowledge, no variation according to ethnicity has been described for TFA. In addition, quantification of TFA is currently not really standardized. Nevertheless, evaluation of TFA seems better and more sensitive than immunological measurements [52]. In addition, TFA quantification is easy to perform since it can be realized on classical hemostasis analyzers, in contrast to TF-exposing EV detection, which needs more sophisticated analyzers such as flow cytometry or ELISA microplate readers. As it was shown that TFPI directly inhibits FXa [53], we added an inhibitory antibody against TFPI to avoid its interference in the assay. Lastly, recent studies suggest that assays that measure TFA in plasma or isolated EVs are less accurate in detecting TF in plasma than those that use an anti-TF antibody to discriminate between TF-dependent and TF-independent FXa generation [54].

In conclusion, consideration of TFA and D-dimer at diagnosis and during the follow-up of patients could be useful to identify LC patients at risk of thrombosis within the next 3 months and could select LC patients who need thromboprophylaxis, which may be better than a KS $\geq$ 2. These findings need to be confirmed in larger prospective studies.

APPENDICES

Collaborators and coinvestigators Severine Fraboulet and Anne Cecile Metivier (Pneumologie, Foch Hospital, Surenses, France); Florent Vinas (Pneumologie, Centre Hospitalier Intercommunal, Créteil, France); Cecile Dujon (Pneumologie, Centre Hospitalier Versailles, Le Chesnay, France); and Mathilde Labro and Alexandre Vallée (Direction de la Recherche Clinique & de l'Innovation, Foch Hospital) for helpful discussions in statistical analyses.

ACKNOWLEDGMENTS

The authors thank Roselyne Bironien for her excellent technical assistance, the Centre de Ressources Biologiques of Foch Hospital for the storage of the plasma samples, Anna Domingues (research nurse), and Polly Gobin for her editorial assistance.

FUNDING

This project did not receive funding.

AUTHOR CONTRIBUTIONS

H.D.: conceptualization, methodology, investigation, resources, and writing the original draft; I.M., R.A., G.M., P.V.D.: resources; J.T.: formal analysis; P.D. and L.-J.C.: conceptualization and methodology; P.G. and C.C.: resources and writing – review; M.V.: conceptualization, methodology, validation, investigation, and writing – review.

RELATIONSHIP DISCLOSURE

H.D. received speaker's fees from Leo Pharma and travel expenses from Leo Pharma, Bristol-Myers Squibb, Novartis, Roche, Takeda, and MSD. I.M., R.A., J.T., P.D., and P.V.D. have no conflict of interest P.G. has received consulting fees, speaker fees, and travel support to attend scientific meetings from Leo Pharma, Bayer, and BMS/Pfizer. L.-J.C. received fees from Novartis, LVL Air Liquide, and travel expenses from Aria Medical. C.C. has received research grants, consulting fees, speaker fees, and travel support from AstraZeneca, GlaxoSmithKline, Roche, Sanofi Aventis, Bristol-Myers Squibb, MSD, Lilly, Novartis, Pfizer, Takeda, Bayer, Leo Pharma, and Amgen. M.V. received speaker fees and travel expenses from Leo Pharma and speaker fees from Bayer.

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SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.rpth.2024.102359