Risk of Venous Thromboembolism in Patients With Stage III and IV Non–Small-Cell Lung Cancer: Nationwide Descriptive Cohort Study

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Abstract

This nationwide cohort study highlights the significant risk of VTE in patients undergoing cancer therapies for NSCLC. The 1-year risk of VTE was highest within the initial 6 months of treatment and demonstrated substantial variability on cancer stage and the specific treatments received. These findings emphasize the importance of a nuanced risk assessment tailored to both cancer stage and the specific cancer therapies employed. Such insights contribute to the ongoing efforts to optimize patient care.

Background: Venous thromboembolism (VTE) is a common complication in patients starting cancer therapies for non–small-cell lung cancer (NSCLC). We examined the risk and timing of VTE in patients with stage IIIA, IIIB to C, and stage IV NSCLC according to received cancer treatments. **Materials and Methods:** A nationwide registry-based cohort study of patients recorded in the Danish Lung Cancer Registry (2010-2021) followed for 1 year after entry into the registry to assess the incidence of VTE. The Aalen–Johansen estimator was used to calculate the risk of VTE after treatment commencement with chemotherapy, radiotherapy, chemoradiation, immunotherapy, and targeted therapy. **Results:** Among the 3475 patients with stage IIIA, 4047 with stage IIIB to C, and 18,082 patients with stage IV cancer, the 1-year risk of VTE was highest in the first 6 months and varied markedly by cancer stage and cancer treatment. In stage IIIA, VTE risk was highest with chemotherapy (3.9%) and chemoradiation (4.1%). In stage IIIB to C, risks increased with chemotherapy (5.2%), immunotherapy (9.4%), and targeted therapy (6.0%). Stage IV NSCLC showed high risk with targeted therapy (12.5%) and immunotherapy (12.2%). The risk was consistently higher for pulmonary embolism than deep vein thrombosis. **Conclusion:** VTE risks vary substantially according to cancer treatments and cancer stages. The highest risk was observed in the initial 6 months of therapy initiation. These insights emphasize the need for tailored risk assessment and vigilance in managing VTE complications in patients with NSCLC. Further research is needed to optimize individual thromboprophylaxis strategies for patients with unresectable and metastatic NSCLC.

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Introduction

Lung cancer remains a common cancer with more than 2 million new cases annually worldwide and a leading cause of cancer death.[1] Venous thromboembolism (VTE), comprising deep vein thrombo-

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sis and pulmonary embolism is common in cancer patients, in part, due to the release of procoagulants by the primary tumor. The risk varies according to the cancer primary but is higher in advanced disease and further increased by cancer therapies such as chemotherapy. Thrombosis is the leading cause of death in cancer outpatients receiving chemotherapy, second only to the cancer itself.[2] The risk of VTE is particularly high in patients with lung cancer,[3] with incidence risks reaching 15% in different treatment regimens.[4-10]

Approximately 80% of patients with lung cancer are diagnosed with non–small-cell lung cancer (NSCLC), of whom 10% to 15% have N2 lymph node involvement (stage IIIA), while ∼55% have advanced disease (stage IIIB-IV).[11] In Denmark, patients with NSCLC and stage IIIA tumors are allocated to chemoradiation with curative intent or surgery followed by adjuvant chemotherapy, while patients with stage IIIB to IV cancer receive palliative therapy,[12] with chemotherapy and immunotherapy as the cornerstone in treatment of advanced NSCLC. The Khorana score stands as a widely acknowledged tool for assessing the risk of VTE in individuals undergoing chemotherapy. It has proven instrumental in identifying patients who stand to gain from primary thromboprophylaxis.[13-15] Nevertheless, the initial iteration of the score did not assign a numerical risk to lung cancer, prompting subsequent analyses that have cast doubt upon its applicability within the context of lung cancer.[4,15,16] The increased use of systemic cancer therapies has seen a parallel increase in the incidence of VTE.[3] This study aims to establish the risk of VTE associated with cancer therapies for stage III and IV NSCLC. The role of primary thromboprophylaxis in lung cancer patients remains unclear, emphasizing the necessity for current knowledge on VTE risks and timing. Our registry-based cohort study investigates the VTE risk and timing based on cancer treatments in a nationwide cohort of stage IIIA, IIIB to C, and IV NSCLC patients.

Methods

Setting and Data Sources

This study was designed as a nationwide cohort study based on existing data from nationwide registries with prospectively collected information from the Danish National Health Service system, which cover the entire nation of nearly 5.8 million residents. The universal health care system in Denmark is tax funded and provides access to primary and secondary health care without additional charge.[17] The nationwide registries track vital status, hospital diagnoses, and procedures for the entire population, facilitating ongoing population surveillance and follow-up. Data can be linked accurately across registries using the unique civil registration number assigned to all residents at birth or immigration. The Danish Lung Cancer Registry has recorded mandatory information on primary lung cancer since 2003 including detailed information on treatment, patient, and clinical characteristics. The Danish National Patient Registry has recorded all inpatient hospitalizations in Denmark since 1977 and outpatient and emergency department visits since 1995 including information on selected treatments and procedures.[18] Information on dispensed prescriptions were collected from the Danish National Prescription Registry.[19] Migration and vital status are tracked by the Civil Registration System since 1968.[20]

Study Population

From the source population of all patients in Denmark with lung cancer identified in the Danish Lung Cancer Registry, we included patients aged ≥18 years diagnosed with NSCLC clinical stage IIIA + B + C and IVA + B tumors between 2010 and 2021 according to the UICC TNM Classification version 8.[21-23] Exclusion criteria were missing information on clinical cancer stage, inconsistent information on date of death, and immigration to Denmark within the year prior to cancer diagnosis. We also excluded patients with a diagnosis of VTE or atrial fibrillation before lung cancer, as well as patients with a dispensed prescription for an oral anticoagulant in the 6 months before lung cancer, as these conditions and medication may affect the thrombosis risk. Patients with a record of cancer therapy (chemotherapy, radiotherapy, immunotherapy, targeted therapy) in the 180 days up to the diagnosis of lung cancer were also excluded.

Patient Characteristics and Cancer Treatment

Information on sex, age, and vital status was obtained from the Danish Civil Registration System. Clinical characteristics from the Danish Lung Cancer Registry included The Eastern Cooperative Oncology Group performance status (ECOG PS) classified as 0, 1, 2, 3 to 4,[24] smoking history as pack years (none, <5, 5-15, >15), and body mass index as mean weight/height^2. Baseline comorbidity comprising a modified Charlson Comorbidity Index that excluded cancer was collected from the Danish National Patient Registry and classified as scores of 0 to 2, and ≥3.[25] We included the following diseases separately: chronic obstructive pulmonary disease, diabetes, hypertension, and cardiovascular disease. From the Danish National Patient Registry, we extracted information on cancer treatments with chemotherapy, radiotherapy, immunotherapy, and targeted therapy (Supplemental Table 1 for codes and definitions). Patients were allocated to a treatment group if there were any record of treatment in the initial 90 days following the date of entry into the Danish Lung Cancer Registry. Chemoradiation was defined as records of both chemotherapy and radiotherapy within the 90-day timeframe, with initiation date set as the date of the last treatment commenced. In instances where multiple treatment types occurred within the 90-day period, treatment groups were not mutually exclusive. Thus, patients could be followed in several treatment groups if they had received multiple treatments.

Venous Thromboembolism Outcomes

Outcomes included VTE defined as deep vein thrombosis and pulmonary embolism, recorded as either primary or secondary inpatient or outpatient diagnoses, with preference to pulmonary embolism when both diagnoses were recorded during the same hospital contact.[26] We also followed patients for pulmonary embolism and deep vein thrombosis as separate endpoints.

Follow-Up

Patients were included in the study at the date of cancer diagnosis, with time at risk for outcome starting at time of cancer treatment initiation identified within 90 days following diagnosis. Thus, the initiation of treatment was considered as the time of delayed

entry. This delayed entry was applied to obtain risk estimates associated with treatment and to mitigate potential bias arising from some patients dying, or getting a VTE diagnosis before the start of cancer treatment. Patients could be included in multiple treatment groups if they had received multiple treatments within the 90-day period. Patients were followed up to 1 year to assess incident VTE and death and censored at emigration from Denmark or end of study (last available data) on 10th May 2022, whichever occurred first. All-cause mortality after treatment initiation was examined as a secondary outcome.

Statistical Analysis

Baseline patient characteristics at entry into the DLCR database were summarized according to clinical cancer stage IIIA, IIIB to C, and IV as proportions for discrete variables and medians with interquartile range for continuous variables.

We conducted stratified analyses specifically within each clinical cancer stage according to commencement of treatment with chemotherapy, radiotherapy, chemoradiation, immunotherapy, and targeted therapy. In each treatment-specific analysis, we excluded patients if they had an incident diagnosis of VTE (in the up to 90 days) between entry into the Danish Lung Cancer Registry and treatment start (Figure 1). The initiation of treatment in each treatment group was considered as the time of delayed entry.

Specifically, we computed incidence rates as number of events per 100 person-years, and cumulative risks using the Aalen–Johansen estimator, accounting for differences in survival time due to the competing risk of death. All-cause mortality was calculated by the Kaplan–Meier failure function.

All analyses were performed with Stata/MP version 17.0 (StataCorp LLC, TX, USA).

Ethics and Data Statement

The study was approved by the Danish Data Protection Agency through institutional registration (ref. 2019-65). Registry studies do not require ethical approval in Denmark. The data were provided by the Danish Health Data Authority, The Danish Clinical Quality Program—National Clinical Registries, and The Danish Lung Cancer Registry. Owing to Danish data protection rules, we are not allowed to share individual level data. Researchers who fulfil the requirements set by the data providers could obtain similar data.

Results

The study population derived from the DLCR included 86,331 lung cancer patients. After exclusion of patients with inconsistent information ($N = 584$), patients aged <18 years at diagnosis ($N = 6$), patients with small cell carcinoma ($N = 12{,}294$), clinical stage I or II cancer ($N = 27{,}395$), previous VTE ($N = 2252$) or atrial fibrillation ($N = 3998$), use of oral anticoagulants in the past 6 months ($N = 594$), lung cancer diagnosis before 2010 ($N = 12{,}890$), and those with cancer treatment in the past 180 days ($N = 714$), the final study population included 25,604 lung cancer patients with clinical stage III or IV NSCLC during 2010 to 2021. A flowchart of the inclusion and exclusion criteria in stage and treatment groups is demonstrated in Figure 1.

Baseline Characteristics

Baseline patient characteristics are shown in Table 1. There were 3475 patients with stage IIIA, 4047 with stage IIIB to C, and 18,082 patients with stage IV NSCLC cancer. Half of all patients were female, and the median age was 70 years. Most characteristics were similar across stage IIIA, IIIB to C, and IV cancer. However, patients with stage IV cancer had a higher comorbidity score and worse ECOG performance status. In the 90 days after lung cancer diagnosis, 60.5% of patients with stage IIIA cancer initiated chemotherapy and 56.0% initiated radiotherapy: 35.6% initiated chemoradiation (defined as chemotherapy and radiotherapy within 90 days), while 3.2% initiated immunotherapy. Among patients with stage IIIB to C tumors, 66.1% received chemotherapy, 58.7% radiotherapy, 41.7% chemoradiation, and 7.0% immunotherapy. In the stage IV group, 53.7% received chemotherapy, 40.7% radiotherapy, and 23.0% chemoradiation, while 13.3% and 4.8%, respectively, received immunotherapy or targeted therapy (Table 1).

Risk of VTE According to Cancer Stage and Treatment

Analyses of VTE risk by cancer treatment are shown in Tables 2 to 4 and Figure 2. The risk of VTE varied with cancer treatments across stages, with a higher risk of pulmonary embolism than deep vein thrombosis in all strata. Most events of VTE occurred in the first 6 months after treatment start. For cancer stage IIIA (Table 2), the risk of VTE was higher with chemoradiation (4.1%) and chemotherapy (3.9%). Most events were pulmonary embolisms (3.2% and 2.8%, respectively). For targeted therapy, there were less than 5 events among the 36 patients initiating treatment, but the risk was high at 5.5%. The incidence rates per 100 person-years were aligned with the risk estimates. The mortality risk was lowest with chemoradiation (19.4%) and highest with immunotherapy (64.7%) (Table 2).

Among patients with stage IIIB to C cancers (Table 3), VTE risk was 9.4% for patients initiating immunotherapy and 6.0% for patients initiating targeted therapy, and chemotherapy (5.2%) and slightly lower for radiotherapy (3.8%). The mortality risk was highest for radiotherapy (49.1%) and lowest for chemoradiation (28.0%).

In stage IV cancer (Table 4), the risk of VTE was substantial for patients starting immunotherapy (12.2%) and targeted therapy (12.5%). In contrast, mortality risk was markedly higher for patients initiating radiotherapy (83.3%) than targeted therapy (39.7%) (Table 3).

Discussion

The findings of this nationwide cohort study of patients with NSCLC in Denmark demonstrated substantial one-year risks of VTE following treatment for stage III and IV NSCLC. The risk of pulmonary embolism consistently exceeded that of deep vein thrombosis. Most thrombotic events occurred in the first 6 months after treatment start. Cancer treatment influenced VTE risk with distinct patterns observed across stages. For patients with stage IIIA, highest risks of VTE were observed with chemotherapy and chemoradiation. Stage IIIB to C displayed high risk with chemotherapy, immunotherapy, and targeted therapy. Notable, patients with stage IV receiving immunotherapy and targeted therapy experienced a marked high risk. Parallel to the VTE risk, the all-cause mortal-

Figure 1 Flow chart of the study population. *Note*: The box "Treatment initiation with 90 days" includes a category of patients with "no treatment" reflecting patients with no treatment initiation within 90 days. The box "No treatment or VTE before treatment" include patients with no treatment initiation within the 90-day period and patients who had a VTE event in the 90-day period. Treatment groups are not mutually exclusive. Patients in the chemoradiation group are also included separately in the chemotherapy and the radiotherapy group. Patients can be included in several treatment groups. Thus, percentages do not necessarily add to 100%. Abbreviations: NSCLC = non–small-cell lung cancer; VTE = venous thromboembolism.

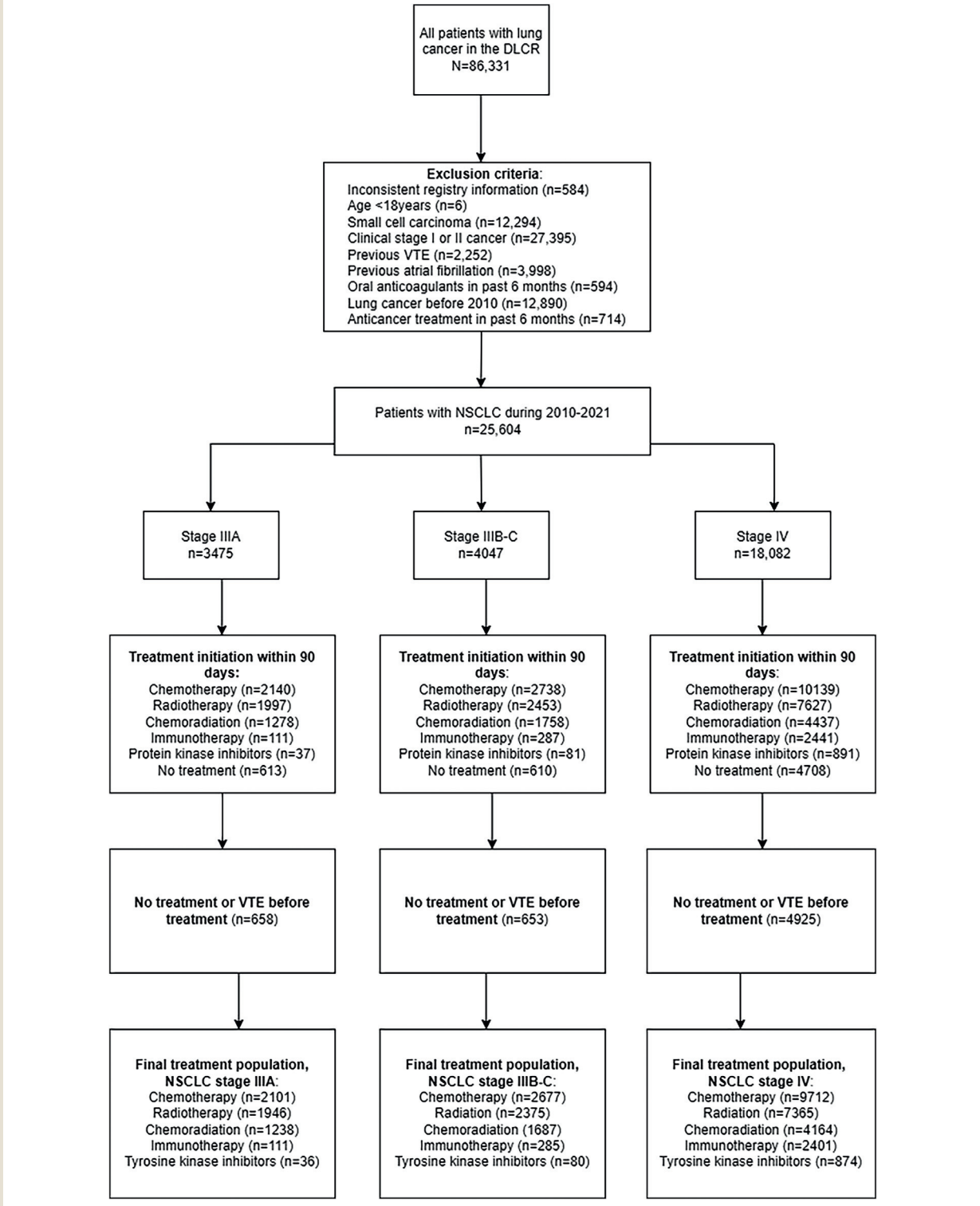


Table 1 Descriptive Characterization of Patients With Primary Stage IIIA, IIIB-C, or IV Non–Small-Cell Lung Cancer During 2010-2021

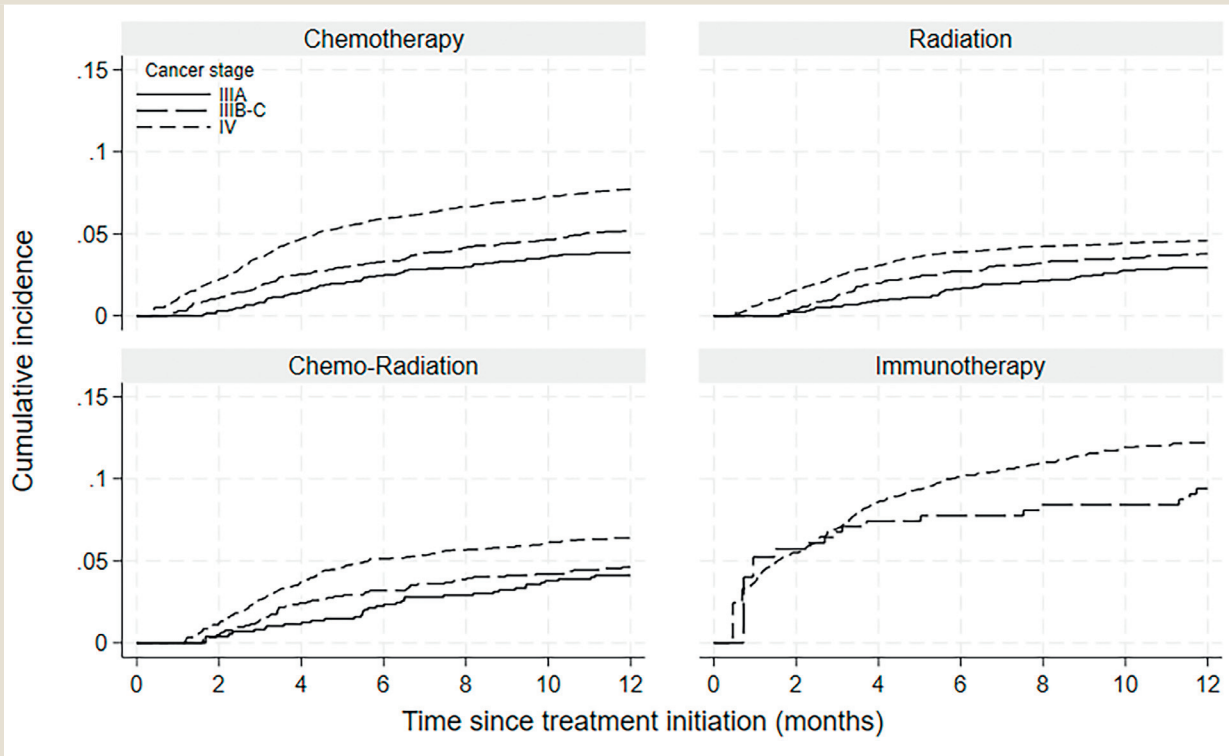
Characteristic	Stage IIIA	Stage IIIB-C	Stage IV
Patients, *N*	3475	4047	18,082
Females	49.7 (1726)	47.6 (1926)	50.5 (9137)
Median age at diagnosis (IQR), y	71.0 (64.0, 77.0)	70.0 (63.0, 77.0)	70.0 (64.0, 77.0)
Age group, y			
<60	13.8 (480)	16.2 (657)	14.9 (2703)
60-69	31.3 (1086)	31.9 (1292)	32.4 (5863)
70-79	38.2 (1327)	35.4 (1431)	36.3 (6571)
≥80	16.7 (582)	16.5 (667)	16.3 (2945)
Charlson index score			
0-2	73.6 (2558)	74.8 (3029)	67.8 (12,262)
≥3	26.4 (917)	25.2 (1018)	32.2 (5820)
Comorbidity			
Chronic obstructive pulmonary disease	18.7 (650)	16.3 (660)	14.4 (2601)
Diabetes	13.8 (480)	12.7 (512)	11.8 (2140)
Hypertension	37.0 (1286)	33.6 (1361)	35.0 (6325)
Cardiovascular disease	17.7 (614)	16.8 (679)	14.6 (2636)
BMI, median (IQR)[a]	24.3 (21.5, 27.5)	24.1 (21.4, 27.0)	23.8 (21.0, 26.9)
ECOG performance status[a]			
0	47.4 (1550)	45.0 (1718)	33.0 (5284)
1	33.6 (1067)	31.4 (1198)	32.6 (5221)
2	13.0 (426)	14.2 (541)	17.3 (2772)
3-4	6.9 (226)	9.5 (361)	17.4 (2783)
Smoking, pack y[a]			
None	4.5 (138)	3.8 (136)	6.6 (958)
<5	0.7 (22)	0.8 (28)	1.2 (177)
5-15	4.2 (128)	4.7 (168)	5.1 (739)
>15	90.7 (2793)	90.8 (3274)	87.2 (12,747)
Diagnosis y			
2010-2012	23.3 (809)	26.8 (1084)	25.1 (4536)
2013-2015	22.7 (788)	24.7 (1001)	24.8 (4479)
2016-2018	26.4 (917)	25.5 (1032)	25.1 (4546)
2019-2021	27.7 (961)	23.0 (930)	25.0 (4521)
Cancer treatment within 90 d			
Chemotherapy	60.5 (2101)	66.1 (2677)	53.7 (9712)
Radiotherapy	56.0 (1946)	58.7 (2375)	40.7 (7365)
Chemoradiation	35.6 (1238)	41.7 (1687)	23.0 (4164)
Immunotherapy	3.2 (111)	7.0 (285)	13.3 (2401)
Targeted therapy	1.0 (36)	2.0 (80)	4.8 (874)

Note: Treatment groups are not mutually exclusive. Patients in the chemoradiation group are also included separately in the chemotherapy and the radiotherapy group. Patients can be included in several treatment groups. Thus, percentages do not necessarily add to 100%.
Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; IQR = Interquartile range.
[a] Among patients with nonmissing: (BMI: 19% missing, *N* = 4882; ECOG performance status: 10% missing, *N* = 2457; pack y history: 17% missing, *N* = 4296).

ity risk demonstrated consistent increase with advancing stages. Lower mortality risk was observed with chemoradiation in stage IIIA and IIIB to C cancers, and with targeted therapy in stage IV cancer.

Our results align with previous studies on the risk of VTE in lung cancer, reporting increased risk with cancer progression,[3,27,28] and risks varying from 5% to 13% in first-line treatment.[4,6,7] Studies have documented 12-month risks following treatment initiation of 5% to 13% for immune checkpoint inhibitors, 7% for chemotherapy, and similarly around 7% in patients with tumor anaplastic lymphoma kinase-rearrangements treated with tyrosine kinase inhibitors.[5,7,10,29] Studies have also indicated that proto-oncogene receptor tyrosine kinase rearrangements, and to some extent, EGFR and Kirsten rat sarcoma viral oncogene positive lung cancers are associated with an increased risk of VTE.[30] As expected, studies incorporating screening for thrombosis have demonstrated higher risk compared with those without screening.[5] Studies have also reported that within specific treatments, the risk of VTE varies with patient and cancer specific risk factors, such as sex, smoking status, and pack year history.[4] Reasons for the variation in VTE risk

Figure 2 Cumulative risk of VTE with cancer treatment in patients with stage IIIA, IIIB-C, and IV non–small-cell lung cancer, Denmark, 2010-2021. *Note*: Follow-up starts on the time of treatment commencement in the 90 days after entry to the Danish Lung Cancer Registry (time zero). Treatment groups are not mutually exclusive. Patients in the chemoradiation group are also included separately in the chemotherapy and the radiotherapy group. Abbreviation: VTE = venous thromboembolism.



across studies may relate to the diverse patient populations studied, with randomized trials based on strict inclusion and exclusion criteria, while most observational studies assessing the VTE risk were conducted as single center or regional studies.[4,5,7]

Our results extend beyond these previous studies by demonstrating varying thrombosis risk with cancer treatment across stages in a nationwide setting. Notably, our findings revealed higher risk of VTE, particularly pulmonary embolism, in treatments associated with higher survival. The cohort of patients with stage IIIA lung cancer, constituting a relatively large patient group often assigned chemoradiation with curative intent, also demonstrated high risk of VTE. Also for patients with stage IIIB to C and IV cancer, a thrombotic event often has serious consequences. Development of VTE can be devastating, potentially leading to interruptions, postponements, or cancellations of vital treatment,[5] thereby affecting lung cancer prognosis, quality of life, morbidity burden, and, in some cases, being fatal.[31]

Some therapies, such as anti-angiogenesis inhibitors, immunotherapies, chemotherapies (particularly platinum-based) are highly thrombogenic agents.[27,28,32] The mechanisms may vary across drug classes. For example, platinum-based chemotherapy may affect the vessels, triggering the release of cytokines and procoagulant factors, whereas immunotherapies may activate the immune system and lead to autoimmune reactions increasing the thrombosis risk.[6,32,33] Substantial evidence supports that VTE can be prevented with anticoagulant therapy in cancer patients.[34,35] However, as anticoagulant treatment increases the risk of bleeding, primary thromboprophylaxis is currently not routinely recommended in cancer.[3,27,28] Additionally, existing risk scores for cancer associated VTE have failed to accurately predict risk in lung cancer.[16,36] Identification of patients who may benefit from thromboprophylaxis therefore remains a research priority. Early identification and treatment of a thrombus is essential for the long-term outcome.[37,38] Therefore, it is imperative that patients are aware of the signs and symptoms, necessitating medical attention and initiation of treatment. Communication with patients about VTE as a common complication is highlighted as a priority in numerous clinical guidelines.[39-41] Yet, patient education regarding the risks of VTE is poor and inconsistent.[42-45]

Strengths and Limitations

Strengths of this study include its nationwide design within a uniform healthcare system providing free access to healthcare. The design and data sources reduce the risk of selection bias arising from selective inclusion of patients. All Danish hospitals and clinics report data on diagnoses including VTE to the Danish National Patient

Table 2 One-Year Rates and Risks of VTE, PE, DVT, and All-Cause Death by Treatment in Patients With Non–Small-Cell Lung Cancer Stage IIIA, Denmark, 2010-2021

		VTE			PE			DVT			Death		
Treatment Initiation	Patients, *N*	Events, *N*	Rate Per 100 PY	Risk, %	Events, *N*	Rate Per 100 PY	Risk, %	Events, *N*	Rate Per 100 PY	Risk, %	Events, *N*	Rate Per 100 PY	Risk, %
Chemotherapy	2101	69	4.94 (3.90, 6.25)	3.9 (3.0, 4.8)	50	3.56 (2.70, 4.69)	2.8 (2.1, 3.6)	21	1.48 (0.97, 2.27)	1.2 (0.8, 1.8)	427	29.96 (27.25, 32.94)	24.5 (22.3, 26.8)
Radiotherapy	1946	49	4.50 (3.40, 5.96)	2.9 (2.1, 3.9)	35	3.20 (2.30, 4.46)	2.1 (1.4, 2.9)	17	1.55 (0.96, 2.49)	1.0 (0.6, 1.6)	471	42.60 (38.93, 46.63)	39.3 (32.6, 46.9)
Chemoradiation	1238	34	5.06 (3.61, 7.08)	4.1 (2.8, 5.7)	26	3.85 (2.62, 5.65)	3.2 (2.1, 4.7)	10	1.47 (0.79, 2.73)	1.2 (0.6, 22.2)	173	25.24 (21.75, 29.30)	19.4 (17.0, 22.2)
Immunotherapy	111	<5	3.66 (1.18, 11.36)	1.3 (0.1, 5.7)	<5	2.44 (0.61, 9.75)	0.9 (0.1, 4.4)	<5	1.22 (0.17, 8.64)	<0.1	31	37.65 (26.48, 53.53)	64.7 (23.9, 98.1)
Targeted therapy	36	<5	8.01 (2.00, 32.01)	5.5 (1.0, 16.1)	<5	8.01 (2.00, 32.01)	5.5 (1.0, 16.1)	0	0.0	0.0	13	50.87 (29.54, 87.61)	36.8 (23.3, 54.8)

Note: Treatment groups are not mutually exclusive. Patients in the chemoradiation group are also included separately in the chemotherapy and the radiotherapy group.
Abbreviations: DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism; PY = person-years.

Table 3 One-Year Rates and Risks of VTE, PE, DVT, and All-Cause Death Overall and by Treatment in Patients With Non–Small-Cell Lung Cancer Stage IIIB-C, Denmark, 2010-2021

		VTE			PE			DVT			Death		
Treatment Initiation	Patients, *N*	Events, *N*	Rate Per 100 PY	Risk, %	Events, *N*	Rate Per 100 PY	Risk, %	Events, *N*	Rate Per 100 PY	Risk, %	Events, *N*	Rate Per 100 PY	Risk, %
Chemotherapy	2677	117	6.57 (5.48, 7.88)	5.2 (4.3, 6.2)	80	4.46 (3.58, 5.55)	3.4 (2.7, 4.2)	37	2.05 (1.48, 2.83)	1.6 (1.1, 2.2)	881	48.38 (45.29, 51.68)	37.1 (35.1, 39.1)
Radiotherapy	2375	72	6.15 (4.88, 7.75)	3.8 (3.0, 4.8)	46	3.89 (2.91, 5.19)	2.4 (1.7, 3.1)	27	2.28 (1.56, 3.32)	1.5 (1.0, 2.1)	794	66.26 (61.88, 71.03)	49.1 (45.7, 52.5)
Chemoradiation	1687	49	5.85 (4.42, 7.74)	4.6 (3.4, 6.1)	34	4.02 (2.87, 5.63)	3.0 (2.1, 4.2)	16	1.88 (1.15, 3.08)	1.7 (0.9, 2.9)	321	37.43 (33.55, 41.75)	28.0 (25.5, 30.7)
Immunotherapy	285	14	6.75 (4.00, 11.40)	9.4 (3.4, 19.1)	12	5.74 (3.26, 10.11)	8.7 (2.9, 18.7)	<5	1.42 (0.46, 4.40)	1.0 (0.3, 2.8)	95	44.56 (36.45, 54.49)	34.2 (28.8, 40.4)
Targeted therapy	80	5	8.67 (3.61, 20.84)	6.0 (2.2, 12.5)	<5	5.20 (1.68, 16.13)	3.6 (1.0, 9.3)	<5	3.38 0.85, 13.52)	2.4 (0.5, 7.6)	23	38.88 (0.85, 13.52)	31.5 (21.6, 44.5)

Note: Treatment groups are not mutually exclusive. Patients in the chemoradiation group are also included separately in the chemotherapy and the radiotherapy group.
Abbreviations: DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism; PY = person-years.

Table 4 One-Year Rates and Risks of VTE, PE, DVT, and All-Cause Death Overall and by Treatment in Patients With Non–Small-Cell Lung Cancer Stage IV, Denmark, 2010-2021

Treatment Initiation	Patients, *N*	VTE			PE			DVT			Death		
		Events, *N*	Rate Per 100 PY	Risk, %	Events, *N*	Rate Per 100 PY	Risk, %	Events, *N*	Rate Per 100 PY	Risk, %	Events, *N*	Rate Per 100 PY	Risk, %
Chemotherapy	9712	536	11.95 (10.98, 13.01)	7.7 (6.6, 8.9)	392	8.65 (7.83, 9.55)	5.8 (4.7, 7.0)	173	3.77 (3.25, 4.38)	2.3 (2.0, 2.7)	4797	103.38 (100.50, 106.35)	64.4 (62.8, 66.0)
Radiotherapy	7365	282	11.91 (10.60, 13.39)	4.6 (4.0, 5.3)	209	8.76 (7.65, 10.04)	3.2 (2.8, 3.8)	87	3.60 (2.92, 4.44)	1.6 (1.1, 2.1)	4784	196.06 (190.59, 201.70)	83.3 (82.2, 84.4)
Chemoradiation	4164	156	13.47 (11.51, 15.76)	6.4 (5.3, 7.6)	114	9.74 (8.10, 11.70)	4.6 (3.7, 5.6)	50	4.22 (3.20, 5.57)	2.1 (1.5, 2.9)	1849	154.12 (147.25, 161.31)	76.0 (73.6, 78.4)
Immunotherapy	2401	203	12.68 (11.05, 14.55)	12.2 (8.1, 17.2)	154	9.50 (8.11, 11.12)	7.8 (6.3, 9.5)	67	4.07 (3.20, 5.17)	5.4 (2.0, 11.4)	1046	62.55 (58.87, 66.46)	44.3 (42.3, 46.3)
Targeted therapy	874	67	11.32 (8.91, 14.38)	12.5 (5.5, 22.4)	51	8.54 (6.49, 11.23)	10.5 (3.8, 21.0)	19	3.13 (2.00, 4.91)	5.3 (1.4, 13.3)	332	54.16 (48.64, 60.32)	39.7 (36.4, 53.2)

Note: Treatment groups are not mutually exclusive. Patients in the chemoradiation group are also included separately in the chemotherapy and the radiotherapy group.
Abbreviations: DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism; PY = person-years.

Registry and on lung cancers to the DLCR. The positive predictive value is >90% for VTE,[46] and 87% for lung cancer diagnoses.[47] Due to our reliance on data from existing registries, any lack of completeness and validity may affect our risk estimates. We did not have information on thromboprophylaxis and on cancer treatment lines. Due to our pragmatic definition of treatments as commencement within 90 days of entry into the DLCR, we may have captured patients initiating treatment lines after the first line and patients switching treatments. We did not have information on combination therapy, or the specific cancer drugs administered. Palliative systemic treatment may extend over a longer period, and the 1-year follow-up period for patients with metastatic disease may be too short to fully capture the burden of treatment-associated thrombosis.[5] We did not have information on causes of death, which may have caused us to underestimate the thrombosis risk. On the other hand, some VTE events may have been asymptomatic and diagnosed incidentally during follow-up scans for cancer.

Conclusion

The findings of this nationwide cohort study demonstrated a high risk of VTE in patients with stage III to IV cancer, highlighting significant variations based on cancer treatments, with the highest risk in the initial 6 months of therapy initiation. These results emphasize the importance of considering VTE as a serious complication in the oncological setting. There is an unmet need to develop valid risk assessment tools and to raise awareness among health care professionals and lung cancer patients regarding the symptoms and signs of VTE. More research is needed to optimize individual thromboprophylaxis strategies for patients with NSCLC and unresectable and metastatic disease.

Clinical Practice Points

- This nationwide registry-based cohort study highlights the significant risk of venous thromboembolism (VTE) in patients undergoing cancer therapies for non-small-cell lung cancer (NSCLC).
- The 1-year risk of VTE was found to be highest within the initial 6 months of treatment initiation and demonstrated substantial variability based on both cancer stage and the specific cancer treatments received.
- Among patients with stage IIIA NSCLC, the highest VTE risks were associated with chemotherapy (3.9%) and chemoradiation (4.1%).
- In stage IIIB to C, elevated risks were observed with chemotherapy (5.2%), immunotherapy (9.4%), and targeted therapy (6.0%).
- Stage IV NSCLC patients faced heightened VTE risks, particularly with targeted therapy (12.5%) and immunotherapy (12.2%).
- Notably, the consistently higher risk for PE compared to DVT underscores the need for targeted monitoring and preventive interventions in this patient population.
- These findings emphasize the importance of a nuanced risk assessment tailored to both cancer stage and the specific cancer therapies employed. Such insights contribute to the ongoing efforts to optimize patient care by identifying and addressing the heightened risk of VTE in individuals undergoing treatment for

NSCLC. Further research and clinical vigilance are warranted to refine risk prediction models and implement timely interventions, ultimately enhancing the overall management and outcomes of NSCLC patients.

Disclosure

Thomas Decker Christensen has been on the speaker bureaus for AstraZeneca, Boehringer–Ingelheim, Pfizer, Roche Diagnostics, Takeda, Merck Sharp & Dohme (MSD) and Bristol–Myers Squibb (BMS) and on Advisory Board for Bayer, Merck MSD, AstraZeneca, and Sanofi. René Horsleben Petersen has received a speaker's fee from Medtronic, AMBU, Medela, and AstraZeneca and on the advisory board for AstraZeneca, Roche, MSD, and BMS. Torben Bjerregaard Larsen reports a relationship with Bayer, Pfizer, Janssen Pharmaceuticals, Roche Diagnostics, and Bristol Meyers Squibb that includes: consulting or advisory. Peter Meldgaard has received research support from Astra Zeneca, MSD, Novartis, Roche, and Takeda; and on advisory board for MSD, Roche, Astra Zeneca, BMS, Takeda, Novartis, and Amgen. Flemming Skjøth has received consultancy fees from Bayer. Simon Noble had received research support and been on speakers bureau from Leo Pharma. Anette Arbjerg Højen has received research grants from the Danish Heart Foundation and The Novo Nordisk Foundation, been on the speaker bureaus for Bayer, Pfizer, MSD, Leo Pharma, and BMS; and on Advisory Board for Bayer and BMS. Other authors: None declared.

CRediT authorship contribution statement

Anne Gulbech Ording: Conceptualization, Data curation, Formal analysis, Visualization, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Thomas Decker Christensen:** Conceptualization, Funding acquisition, Investigation, Resources, Writing – original draft, Writing – review & editing. **Flemming Skjøth:** Conceptualization, Data curation, Formal analysis, Visualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Simon Noble:** Conceptualization, Investigation, Writing – review & editing. **Anette Arbjerg Højen:** Investigation, Writing – review & editing. **Amalie Lambert Mørkved:** Investigation, Writing – review & editing. **Torben Bjerregaard Larsen:** Investigation, Resources, Writing – review & editing. **Rene Horsleben Petersen:** Investigation, Writing – review & editing. **Peter Meldgaard:** Investigation, Writing – review & editing. **Erik Jakobsen:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Mette Søgaard:** Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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Supplementary material

Supplemental Table 1 Codes and Definitions Used in the Study

Chemotherapy	BAHL BBHL BCHL BDHL BEHL BGHL BHHL BIHL BJHL BLHL BNHL BOHL BWHA1 BWHA2 BWHA3 ZWCC0 ML01A ML01B ML01C ML01D
Radiotherapy	BAG BCC BDG BEG BGG BHG BIG BJG BLG BOG BWGC BWGE BWGG BWGJ BNGE BNGF KAAG50
Immunotherapy	BOHJ
Targeted therapy	BWHA4
VTE	I26 I801 I802 I803 I808 I809 I828 I829 I822 I823 0223 0229 0871 0882
Charlson Comorbidity Index	I21 I22 I23 I50 I110 I130 I132 I70 I71 I72 I73 I74 I77 I60 I61 I62 I63 I64 I65 I66 I67 I68 I69 G45 G46 F00 F01 F02 F03 F051 G30 J40 J41 J42 J43 J44 J45 J46 J47 J60 J61 J62 J63 J64 J65 J66 J67 J684 J701 J703 J841 J920 J961 J982 J983 M05 M06 M08 M09 M30 M31 M32 M33 M34 M35 M36 D86 K221 K25 K26 K27 K28 B18 K700 K701 K702 K703 K709 K71 K73 K74 K760 E100 E101 E109 E110 E111 E119 G81 G82 I12 I13 N00 N01 N02 N03 N04 N05 N07 N11 N14 N17 N18 N19 Q61 E102 E103 E104 E105 E106 E107 E108 E112 E113 E114 E115 E116 E117 E118 B150 B160 B162 B190 K704 K72 K766 I85 B21 B22 B23 B24
Chronic pulmonary disease	J44
Obesity	E65 E66 E67 E68
Hypertension	I10 I11 I12 I13 I15
Cardiovascular disease	I48 I20 I21 I23 I24 I25 I46

Abbreviation: VTE = venous thromboembolism.