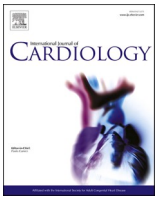
International Journal of Cardiology 390 (2023) 131271

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Risk of recurrent cancer-associated venous thromboembolism: A Danish nationwide cohort study

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ARTICLE INFO

Keywords:
Venous thromboembolism
Recurrence
Mortality
Neoplasm
Epidemiology

ABSTRACT

Background: Predictive factors for recurrent cancer-associated venous thromboembolism have been inconsistent across previous studies. To provide data for improved risk stratification, we described the risk of recurrent venous thromboembolism overall and across age, sex, calendar period, cancer type, Ottawa risk score, cancer stage, and cancer treatment in a nationwide cohort of patients with active cancer.

Methods: Using Danish administrative registries, we identified a cohort of all adult patients with active cancer and a first-time diagnosis of venous thromboembolism during 2003–2018. We accounted for the competing risk of death and calculated absolute risks of recurrent venous thromboembolism at six months.

Results: The population included 34,072 patients with active cancer and venous thromboembolism. Recurrence risks at six months were higher for patients with genitourinary cancer (6.5%), lung cancer (6.1%), gastrointestinal cancer (5.6%), brain cancer (5.2%), and hematological cancer (5.1%) than for patients with gynecological cancer (4.7%), breast cancer (4.1%), and other cancer types (4.8%). Recurrence risks were similar for men (5.2%) and women (4.9%), with and without chemotherapy (5.1%), across Ottawa risk score group (low: 5.0%; high: 5.1%) and across calendar periods but increased with increasing cancer stage. The overall six-month all-cause mortality risk was 26%, and highest for patients with lung cancer (49%) and lowest among breast cancer patients (4.1%).

Conclusions: Six-month recurrence risk after first-time cancer-associated venous thromboembolism was high and varied by cancer type and patient characteristics. Refining risk stratification for recurrence may improve decision-making regarding treatment duration after cancer-associated thromboembolism.

1. Introduction

Cancer and venous thromboembolism are two closely related major public health illnesses associated with reduced quality of life, distress, poor prognosis, and early death [1–3]. A substantial body of evidence supports an association between cancer-specific risk factors and incident venous thromboembolism, including metastatic disease and presence of thrombogenic tumor types [2–4]. The incidence of venous thromboembolism is particularly high for patients treated with certain systemic anticancer treatments [4–6]. Still, in cancer patients, recurrent venous

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https://doi.org/10.1016/j.ijcard.2023.131271
Received 25 May 2023; Received in revised form 24 July 2023; Accepted 14 August 2023
Available online 15 August 2023

thromboembolism remains frequent at 4%–9%, particularly in the first six months after the initial venous thromboembolic event [7–11]. To increase knowledge regarding patient specific risk profiles, we investigated the risk of recurrent venous thromboembolism according to cancer specific factors in a nationwide cohort of Danish patients with active cancer and first-time venous thromboembolism.

2. Methods

We used existing nationwide databases with prospectively collected information from the universal Danish health care system covering the entire nation of approximately 5.8 million people. All residents have access to tax-supported primary and secondary health care free of additional charge and with partial reimbursement for prescribed medications [12]. By linking these nationwide registries, we conducted a population-based cohort study of patients with cancer-associated venous thromboembolism.

2.1. Data sources

Vital status and hospital diagnoses and procedures are tracked by nationwide registries for the entire population. Data can be linked across registries using a unique identifier assigned to all Danish residents at birth or upon immigration. The Danish Cancer Registry includes required information on all primary cancer diagnoses in Denmark since 1987, including the stage and morphology at diagnosis [13]. The Danish National Patient Registry covers all Danish hospitals with clinical inpatient discharge diagnoses since 1977 and diagnoses made at outpatient clinic visits since 1995 [14]. Diagnoses used for this study were coded according to the *Tenth Revision of the International Classification of Diseases* (ICD-10) in use since 1994 [14]. The Danish National Prescription Database has recorded information on prescription claims from outpatient pharmacies since 1994 using the Anatomical Therapeutic Chemical (ATC) Classification System [15]. Migration, sex, and vital status are continuously tracked in the Civil Registration System [16].

2.2. Study population

From the source population consisting of individuals with cancer aged at least 18 years and residing in Denmark between 2003 and 2018, we identified all patients with cancer and venous thromboembolism defined as any in- or outpatient diagnosis of deep vein thrombosis or pulmonary embolism in the Danish National Patient Registry (N = 54,061). We restricted the cohort to patients with active cancer (N = 34,072). Active cancer was defined as a cancer diagnosis (except non-melanoma skin cancer) or metastasis within 180 days before venous thromboembolism recorded in the Danish Cancer Registry or the Danish National Patient Registry. Active cancer was also defined as a record of systemic anticancer therapy (chemotherapy, immune-based therapies, and endocrine therapies) or radiotherapy within the past 180 days before incident venous thromboembolism and a history of cancer (Supporting Information Table 1 for codes).

2.3. Patient characteristics and follow-up

The Danish National Patient Registry and the Danish Cancer Registry was used to characterize the medical history of patients overall and according to primary tumor site classified and grouped as hematological, gastrointestinal, urologic, breast, gynecologic, lung and respiratory tract, brain and central nervous system, and other solid tumors. Analytic variables included type of incident venous thromboembolism (deep venous thrombosis or pulmonary embolism), diagnoses of comorbidities, the Charlson Comorbidity Index Score [17], and the Ottawa score, a point-based risk score developed to estimate risk of recurrence of venous thromboembolism in patients with cancer [18]. This score was utilized to provide further evidence for the usefulness of this score in predicting recurrent venous thromboembolism. Ottawa score components include female sex (1 point), lung cancer (1 point), breast cancer (−1 point), localized stage cancer (−2 points), and was classified according to the clinical probability of recurrences as low score (≤0 points) and high score (≥1 points) in line with the original categorization [18]. Outpatient prescription claims and hospital records of anticoagulant therapy in the three months before and after first-time venous thromboembolism were collected from the Danish National Prescription Registry and the Danish National Patient Registry [14,15]. Surgery and cancer treatment recorded in the Danish National Patient Registry during the six months before first-time venous thromboembolism diagnosis included chemotherapy, radiotherapy, endocrine therapies, and immune-based therapies. Cancer stage was defined for solid tumors as localized, regional, distant, and missing/unknown.

We followed patients who survived the first 10 days after their first-time venous thromboembolism diagnosis to the first subsequently recorded diagnosis of venous thromboembolism, death, emigration from Denmark or end of 2018, whichever came first. This approach was used to reduce inclusion of repeated coding of the incident event in alignment with previous studies [19]. Therefore, patients contributed with person-time in the analysis from the 11th day after first-time venous thromboembolism. To verify the recurrent event, we only included diagnoses with a chest computed tomography scan or ultrasound of the leg recorded within 10 days before or 10 days after the recurrent diagnosis [20].

2.4. Statistical analysis

We described baseline characteristics of patients with active cancer at diagnosis of first-time venous thromboembolism by cancer type. Time to event analyses were applied to estimate risk of recurrence and all-cause mortality. We computed the cumulative risk of recurrent venous thromboembolism from the 11th day after first-time venous thromboembolism by accounting for differential survival time between groups using the Aalen Johansen estimator. Analyses were reported at six months and at 1 year follow-up. Recurrence risks were computed overall and by cancer type within strata of sex, age groups, calendar period, Ottawa score, cancer stage, and anticancer treatment. **To examine the associations between these baseline characteristics and risk of recurrence, we constructed** Fine and Gray regression models accounting for overall survival time, with adjustment for sex and age group.

As a sensitivity analysis, we also computed outcomes using the revised version of the Ottawa score by classifying the recurrence risk as low (≤1 points), intermediate (0 points), and high risk (≥1 points).

2.5. Ethics

The study was conducted in compliance with the General Data Protection Regulation Article 30, recorded at Aalborg University Hospital and Aalborg University (record no: 2017–509-00006). Danish law does not require ethical approval or informed consent from patients in studies based on routinely collected registry data.

3. Results

From 2003 through 2018, we identified 34,072 patients with a first-time diagnosis of venous thromboembolism and active cancer (53% female and median age 72 years) (Table 1). Of this cohort, 16% were diagnosed with brain cancer, 11% with gastrointestinal cancer, 10% with breast cancer, 7.8% with lung cancer, 6.5% with hematological cancer, 6.4% with gynecological cancer, 4.6% with genitourinary cancer, and 37% with other cancer types. Overall, 55% of the cancer cohort was diagnosed with deep vein thrombosis and 45% with pulmonary embolism (2.6% with both diagnoses). Pulmonary embolism was more

Table 1
Characteristics (%, N) of 34,072 patients with first-time cancer-associated venous thromboembolism by cancer type.

	Cancer type							
Characteristic	Hematological	Gastrointestinal	Genitourinary	Gynecologic	Breast	Lung cancer	Brain and CNS	Other solid
Participants, N	2210	3798	1577	2173	3515	2666	5439	12,694
Women	43 (949)	47 (1799)	26 (413)	100.0 (2173)	99 (3477)	48 (1276)	26 (1392)	53 (6679)
Age, years								
Median (IQR)	71.0 (62.0–79.0)	74.0 (67.0–82.0)	71.0 (62.0–79.0)	73.0 (63.0–82.0)	74.0 (65.0–82.0)	70.0 (63.0–76.0)	72.0 (65.0–79.0)	72.0 (64.0–81.0)
18–49	9.8 (217)	2.7 (102)	6.8 (107)	7.8 (170)	5.3 (185)	3.3 (89)	5.4 (295)	5.2 (658)
50–59	10 (230)	8.0 (302)	12 (182)	12 (249)	11 (371)	12 (317)	9.7 (527)	11 (1384)
60–69	25 (549)	22 (854)	26 (409)	21 (450)	22 (767)	32 (849)	24 (1329)	25 (3127)
70–79	32 (710)	34 (1272)	34 (534)	29 (619)	30 (1054)	37 (989)	36 (1947)	31 (3892)
80–89	20 (438)	27 (1020)	19 (295)	25 (541)	25 (893)	14 (384)	21 (1142)	22 (2841)
90+	3.0 (66)	6.5 (248)	3.2 (50)	6.6 (144)	7.0 (245)	1.4 (38)	3.7 (199)	6.2 (792)
Calendar period								
2003–2006	13 (290)	16 (621)	16 (255)	19 (415)	18 (615)	15 (388)	14 (758)	16 (2042)
2007–2010	20 (437)	23 (853)	21 (338)	23 (500)	24 (836)	21 (570)	20 (1107)	21 (2677)
2011–2014	30 (670)	27 (1035)	26 (413)	27 (575)	27 (932)	27 (726)	29 (1577)	29 (3688)
2015–2018	37 (813)	34 (1289)	36 (571)	31 (683)	32 (1132)	37 (982)	37 (1997)	34 (4287)
Type of venous thrombosis								
Deep vein thrombosis	58 (1283)	52 (1989)	61 (963)	61 (1314)	60 (2109)	41 (1087)	57 (3109)	55 (6997)
Pulmonary embolism	42 (927)	48 (1809)	39 (614)	40 (859)	40 (1406)	59 (1579)	43 (2330)	45 (5697)
Charlson score								
0	51 (1119)	49 (1848)	47 (746)	53 (1156)	51 (1784)	45 (1197)	51 (2780)	51 (6418)
1	24 (523)	26 (973)	23 (361)	24 (521)	26 (907)	28 (740)	25 (1341)	25 (3149)
2	13 (295)	13 (487)	14 (227)	13 (273)	12 (424)	14 (373)	13 (690)	13 (1682)
3+	12 (273)	13 (490)	15 (243)	10 (223)	11 (400)	13 (356)	12 (628)	11 (1445)
Individual comorbidities								
Myocardial infarction	5.5 (122)	6.5 (246)	8.2 (129)	4.8 (105)	4.9 (172)	8.1 (216)	7.4 (401)	6.6 (837)
Congestive heart failure	8.2 (181)	9.0 (340)	8.8 (138)	7.6 (166)	8.4 (294)	8.3 (221)	7.3 (396)	8.1 (1034)
Peripheral vascular disease	7.8 (173)	8.5 (324)	11 (168)	7.3 (159)	7.0 (246)	13 (339)	8.4 (455)	8.5 (1076)
Cerebrovascular disease	12 (256)	13 (486)	13 (201)	12 (249)	14 (479)	13 (345)	14 (765)	13 (1646)
Dementia	1.5 (33)	3.0 (114)	2.3 (36)	3.9 (84)	4.4 (154)	1.1 (29)	2.2 (120)	3.0 (384)
Chronic pulmonary disease	14 (311)	14 (535)	15 (235)	13 (280)	17 (589)	27 (731)	13 (685)	15 (1879)
Connective tissue disease	6.3 (139)	4.9 (186)	4.2 (66)	6.4 (139)	8.0 (281)	5.3 (142)	4.9 (269)	5.9 (744)
Ulcer disease	5.0 (111)	8.0 (303)	5.5 (86)	5.0 (108)	4.9 (172)	6.1 (163)	5.6 (305)	5.3 (669)
Liver disease	1.8 (39)	3.0 (113)	1.9 (30)	1.5 (32)	1.9 (66)	2.3 (62)	1.0 (54)	1.8 (226)
Diabetes	9.5 (211)	12 (464)	11 (176)	10 (226)	9.3 (336)	9.4 (251)	11 (614)	10 (1278)
Moderate to severe renal disease	8.8 (194)	6.1 (232)	12 (186)	5.2 (114)	3.8 (135)	3.9 (105)	6.4 (346)	5.3 (677)
Alcoholism or alcohol-related disease	3.1 (69)	5.0 (190)	4.8 (75)	2.4 (52)	2.8 (100)	4.8 (127)	3.5 (190)	3.5 (444)
Obesity	5.2 (116)	6.4 (242)	6.4 (101)	17 (367)	8.5 (299)	3.9 (103)	5.7 (309)	5.7 (718)
Atrial fibrillation	13 (279)	13 (489)	11 (168)	11 (228)	12 (401)	12 (320)	11 (596)	12 (1547)
Ottawa score								
-3	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	22 (1245)	0.0 (0)
-2	2.4 (53)	20 (755)	38 (596)	0.0 (0)	0.4 (15)	0.0 (0)	13 (686)	2.7 (349)
-1	3.0 (67)	19 (716)	13 (208)	51 (1099)	49 (1720)	16 (415)	52 (2802)	2.8 (354)
0	55 (1208)	33 (1244)	36 (568)	0.0 (0)	0.7 (23)	13 (347)	13 (706)	45 (5666)
1	40 (882)	29 (1083)	13 (205)	49 (1074)	50 (1757)	37 (975)	0.0 (0)	50 (6325)
2	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	35 (929)	0.0 (0)	0.0 (0)
Ottawa score group, original								
Low (score ≤ 0)	60 (1328)	72 (2715)	87 (1372)	51 (1099)	50 (1758)	29 (762)	100 (5439)	50 (6369)
High (score ≥ 1)	40 (882)	29 (1083)	13 (205)	49 (1074)	50 (1757)	71 (1904)	0	50 (6325)
Ottawa score group, revised								
Low (score ≤ -1)	5.4 (120)	39 (1471)	51 (804)	51 (1099)	49(1735)	16 (415)	87 (4733)	5.5 (703)
Intermediate (score $= 0$)	54 (1208)	33 (1244)	36 (568)	0 (0)	0.7 (23)	13 (347)	13 (706)	45 (5666)
High (score ≥ 1)	40 (882)	29 (1083)	13 (205)	49 (1074)	50 (1757)	71 (1904)	0 (0)	50 (6325)
Cancer stage, solid tumors								
Localized	NA	39 (1471)	51 (804)	51 (1099)	49 (1735)	29 (762)	35 (1931)	5.5 (703)
Regional	NA	27 (1005)	7.0 (110)	8.8 (191)	26 (923)	25 (660)	7.7 (421)	4.9 (622)
Distant	NA	14 (545)	8.4 (133)	4.7 (103)	2.6 (93)	15 (394)	12 (664)	38 (4776)
Missing/unknown	NA	21 (777)	34 (530)	36 (780)	22 (764)	32 (850)	45 (2423)	52 (6593)
Surgery*	35 (762)	45 (1714)	45 (716)	39 (850)	32 (1107)	33 (878)	38 (2080)	34 (4300)
Cancer treatment*								
Chemotherapy	44 (978)	29 (1089)	14 (227)	23 (506)	14 (485)	40 (1054)	19 (1029)	26 (3348)
Radiotherapy	5.2 (115)	4.1 (155)	5.8 (92)	6.4 (138)	7.1 (248)	20 (519)	9.3 (508)	11 (1411)
Endocrine therapy	1.1 (24)	1.1 (43)	1.3 (21)	1.4 (30)	26 (918)	1.4 (37)	16 (881)	5.1 (647)
Immunotherapy	25 (550)	5.2 (199)	0.4 (7)	2.0 (44)	2.8 (99)	2.0 (54)	2.1 (112)	5.9 (755)
Anticoagulant therapy**								
Heparin	12 (274)	20 (756)	16 (250)	18 (386)	12 (434)	27 (712)	19 (1054)	20 (2557)
Oral anticoagulants	41 (920)	48 (1824)	50 (790)	5 (966)	51 (1805)	33 (890)	48 (2629)	44 (5610)

Data presents the % (number of patients) or the median (interquartile range), as indicated.
* Within six months before diagnosis. CNS. Central nervous system.
** Within three months before and after first-time diagnosis of VTE.

common in patients with lung cancer (59%), whereas deep vein thrombosis was more common among patients with genitourinary (61%), gynecological cancer (61%), and breast cancer (60%). In the six months prior to diagnosis of first-time venous thromboembolism, a history of chemotherapy was most frequent among patients with hematological cancer (44%) and lung cancer (40%). A majority of patients (61%) was categorized according to the Ottawa low risk score group, but with much variation across cancer types.

3.1. Recurrent venous thromboembolism and mortality

As shown in Table 2, we identified 1755 recurrent venous thromboembolic events within 1 year, of which 1352 were diagnosed during the first six months of follow-up. The recurrence risk was 5.1% at six months and 6.7% at one year. The mortality risk during follow-up overall was 26% at six months and 36% at one year, and highest for patients with lung cancer at both six months and one year (data not shown).

3.2. Recurrent venous thromboembolism according to baseline characteristics

Recurrence risks by patient characteristics overall are shown in Table 2 and Fig. 1, and sub-distribution hazard ratios associating baseline characteristics with recurrence are shown in Supporting Information Fig. 1. After six months, the recurrence risk was almost similar for men and women (5.2% and 4.9%) and across Ottawa risk score group: 5.0% for low risk and 5.1% for high risk [subdistribution hazard ratio: 1.12, 95% confidence interval (CI): 0.97, 1.30]. Results were similar using the revised version of the Ottawa score with risk of 4.8% in the low-risk group, 5.2% in the intermediate-risk group, and 5.1% in the high-risk group. Recurrence risks increased slightly with cancer stage from 4.7% for localized stage to 6.3% for distant cancers. Recurrence risks were also similar during follow-up with receipt of surgery (5.3%)

Table 2
Risk of recurrence at 6 months and 1 year after first-time cancer-associated venous thromboembolism by descriptive characteristics at baseline.

	6 months			1 year		
Characteristic	Events, N	Risk, % (95% CI)	sHR (95% CI)*	Events, N	Risk, % (95% CI)	sHR (95% CI)*
All	1352	5.1 (4.8, 5.3)	–	1755	6.7 (6.4, 7.0)	–
Sex						
Men	644	5.2 (4.9, 5.6)	Reference	852	7.0 (6.6, 7.5)	Reference
Women	708	4.9 (4.6, 5.3)	0.94 (0.84, 1.04)	903	6.3 (5.9, 6.7)	0.90 (0.82, 0.99)
Age						
18–49	90	6.0 (4.8, 7.2)	Reference	112	7.4 (6.2, 8.8)	Reference
50–59	166	5.7 (4.9, 6.6)	0.96 (0.74, 1.24)	212	7.4 (6.5, 8.4)	0.98 (0.78, 1.24)
60–69	382	5.9 (5.3, 6.5)	0.99 (0.78, 1.24)	494	7.7 (7.1, 8.4)	1.02 (0.83, 1.26)
70–79	453	5.3 (4.8, 5.7)	0.88 (0.70, 1.10)	587	6.9 (6.4, 7.5)	0.91 (0.74, 1.12)
80+	261	3.6 (3.2, 4.1)	0.60 (0.48, 0.77)	350	4.9 (4.4, 5.5)	0.65 (0.52, 0.80)
Calendar period						
2003–2006	225	5.2 (4.6, 5.9)	Reference	276	6.4 (5.7, 7.2)	Reference
2007–2010	280	4.8 (4.3, 5.4)	0.92 (0.77, 1.10)	351	6.0 (5.4, 6.7)	0.94 (0.80, 1.16)
2011–2014	388	5.0 (4.6, 5.5)	0.96 (0.82, 1.13)	525	6.8 (6.3, 7.4)	1.06 (0.92, 1.23)
2015–2018	459	5.2 (4.8, 5.7)	0.99 (0.84, 1.16)	603	7.1 (6.6, 7.7)	1.09 (0.94, 1.26)
Ottawa score						
-3	46	4.7 (3.5, 6.1)	Reference	64	6.5 (5.1, 8.2)	Reference
-2	105	5.5 (4.5, 6.5)	1.22 (0.86, 1.72)	130	6.8 (5.8, 8.0)	1.08 (0.80, 1.46)
-1	266	4.6 (4.1, 5.2)	1.06 (0.76, 1.46)	352	6.2 (5.6, 6.8)	1.00 (0.76, 1.32)
0	396	5.2 (4.8, 5.8)	1.14 (0.84, 1.55)	532	7.1 (6.6, 7.7)	1.10 (0.85, 1.43)
1	493	5.0 (4.6, 5.5)	1.21 (0.86, 1.69)	625	6.5 (6.0, 7.0)	1.10 (0.82, 1.46)
2	46	6.5 (4.8, 8.5)	1.58 (1.02, 2.45)	52	7.3 (5.5, 9.4)	1.29 (0.87, 1.90)
Ottawa score group						
≤0	813	5.0 (4.7, 5.4)	Reference	1078	6.7 (6.4, 7.1)	Reference
≥1	539	5.1 (4.7, 5.6)	1.12 (0.97, 1.30)	677	6.5 (6.1, 7.0)	1.07 (0.94, 1.21)
Ottawa score group, revised						
Low (score ≤ −1)	417	4.8 (4.4, 5.3)	Ref	546	6.4 (5.9, 6.9)	Ref
Intermediate (score = 0)	396	5.2 (4.8, 5.8)	1.03 (0.89, 1.20)	532	7.1 (6.6, 7.7)	1.06 (0.94, 1.21)
High (score ≥ 1)	539	5.1 (4.7, 5.6)	1.12 (0.97, 1.30)	677	6.5 (6.1, 7.0)	1.08 (0.95, 1.23)
Cancer type						
Hematologic	93	5.1 (4.1, 6.1)	1.02 (0.82, 1.28)	121	6.6 (5.5, 7.8)	1.00 (0.83, 1.22)
Gastrointestinal	164	5.6 (4.8, 6.4)	1.19 (0.99, 1.42)	221	7.6 (6.7, 8.6)	1.20 (1.03, 1.40)
Genitourinary	80	6.5 (5.2, 8.0)	1.35 (1.06, 1.71)	99	8.2 (6.7, 9.8)	1.24 (1.00, 1.54)
Gynecological	80	4.7 (3.7, 5.7)	0.96 (0.75, 1.22)	106	6.2 (5.1, 7.4)	1.00 (0.81, 1.23)
Breast	115	4.1 (3.4, 4.9)	0.85 (0.69, 1.05)	159	5.7 (4.9, 6.6)	0.92 (0.76, 1.10)
Lung	125	6.1 (5.1, 7.2)	1.26 (1.03, 1.53)	144	7.1 (6.0, 8.2)	1.10 (0.92, 1.31)
Brain	218	5.2 (4.5, 5.9)	1.08 (0.91, 1.27)	274	6.6 (5.8, 7.4)	1.01 (0.87, 1.16)
Other	477	4.8 (4.4, 5.2)	Reference	631	6.4 (6.0, 6.9)	Reference
Cancer stage, solid tumors*						
Localized	322	4.7 (4.2, 5.2)	Reference	424	6.3 (5.7, 6.9)	Reference
Regional	162	5.1 (4.4, 6.0)	1.09 (0.91, 1.32)	206	6.6 (5.8, 7.5)	1.06 (0.89, 1.25)
Distant	332	6.3 (5.7, 7.0)	1.33 (1.14, 1.56)	406	7.7 (7.0, 8.5)	1.24 (1.08, 1.42)
Cancer treatment (yes vs. no)						
Chemotherapy	363	5.1 (4.6, 5.7)	0.95 (0.84, 1.08)	454	6.5 (5.9, 7.1)	0.92 (0.82, 1.02)
Radiotherapy	124	5.0 (4.2, 5.9)	0.95 (0.79, 1.14)	150	6.1 (5.2, 7.1)	0.88 (0.74, 1.04)
Endocrine therapy	92	4.5 (3.7, 5.5)	0.89 (0.72, 1.10)	120	5.9 (4.9, 7.0)	0.89 (0.74, 1.07)
Immunotherapy	82	5.4 (4.4, 6.7)	1.04 (0.83, 1.30)	105	7.0 (5.8, 8.4)	1.03 (0.84, 1.25)

Sub-distribution hazard ratios are unadjusted for analyses by Ottawa score and Ottawa score group, otherwise adjusted for sex and age group, except for the association with sex (only adjusted for age group) and age group (only adjusted for sex). Cancer treatment groups are compared with groups of patients without the specific treatment. CI. Confidence interval; sHR. Sub-distribution hazard ratio.

* Proportion of non-missing.

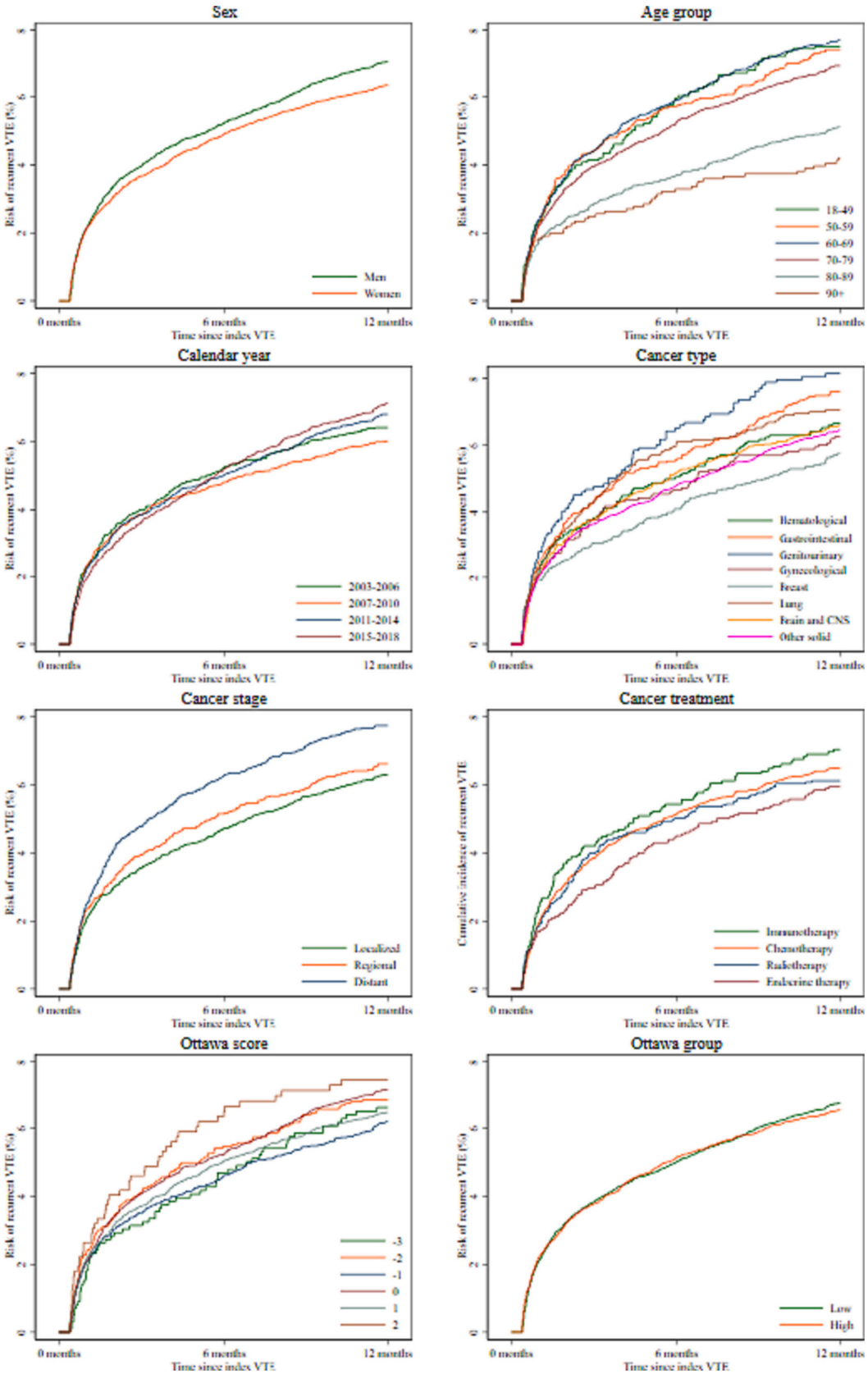

Fig. 1. Risk of recurrence at 1 year after first-time cancer-associated venous thromboembolism by baseline characteristic.

(data not shown), and anticancer treatment: 5.1% for chemotherapy, 5.0% for radiotherapy, 4.5% for endocrine therapy, and 5.4% for immunotherapy at six months.

3.3. Recurrent venous thromboembolism according to cancer types and characteristics

Compared with the overall cohort risk of recurrence of 5.2% at six months, risks were 6.5% for patients with genitourinary cancer, 6.1% for lung cancer, 5.6% for gastrointestinal cancer, 5.2% for brain cancer, 5.1% for hematological cancer, 4.7% for gynecological cancer, 4.1% for breast cancer, and 4.8% for other cancer types (Table 2). The association between age and recurrence varied across cancer types (Supporting Information Tables 2 through 9). For example, for patients with gastrointestinal, gynecological, lung, and brain cancer, the recurrence risk decreased by increasing age group. For patients with breast cancer, recurrence risks were lower among the youngest and oldest age groups (3.1% and 3.6%, respectively) at six months, and higher in the group of patients aged 60–69 years (5.2%). For patients with genitourinary cancer, recurrence risk was near similar across age groups. Risks were not noticeably increased for patients who had received chemotherapy prior to first-time venous thromboembolism (Supporting Information Tables 2 to 9). The dichotomized Ottawa risk score did not predict recurrence risk for any cancer type. For patients with breast cancer and a high Ottawa score, the relative risk of recurrence was 0.85 (0.59, 1.22) compared with breast cancer patients in the low-risk category (Supplemental Information Table 6).

4. Discussion

The incidence of recurrent venous thromboembolism in Danish patients with first-time cancer-associated venous thromboembolism was 5.2% in the first six months, increasing to 6.7% at one year. Overall, recurrence risk was similar for both sexes and was not particularly increased for patients who had received chemotherapy prior to the first-time event but increased slightly by cancer stage. Recurrence risks were higher for patients with genitourinary and lung cancer than patients with breast cancer. Mortality risk was substantial, with more than one-third of all patients dying in the year following first-time cancer-associated venous thromboembolism.

Our results demonstrate recurrent venous thromboembolism risks ranging from 4.1% for breast cancer to 6.6% for genitourinary cancer in the initial six months, increasing to 5.7% and 8.2%, respectively, at 12 month follow-up which is in accordance to other studies. [7–11] Cancer types such as lung, pancreatic, gastric, and brain cancer have been linked with a marked higher incidence of first-time cancer-associated venous thromboembolism, but not necessarily with recurrent venous thromboembolism [21]. In this study, the recurrence risks were not notably higher for patients with these cancer types. Similarly, active cancer treatment is associated with increased risk of first-time venous thromboembolism [2], but was not particularly associated with recurrence.

Guidelines recommend anticoagulant treatment for cancer-associated venous thromboembolism, and a prolonged treatment course for those at increased risk of recurrence [22,23], but at the expense of an increased bleeding risk. However, evidence supporting treatment beyond the initial 6-month period is scarce [24]. Secondary prophylaxis with anticoagulants reduces the recurrence risk by a ratio of 0.43 [25]. Still, recurrence incidences as high as 20% at one year after the first-time events have been reported in some patient populations [21]. Additionally, a meta-analysis demonstrated a recurrence rate of 23.7 cases per 100 person-years [26]. Another meta-analysis reported a recurrence risk of 1 to 12% during the 6 to 12 month period after first-time venous thromboembolism, and of 15% in patients with residual thrombosis at six months randomized to receive no anticoagulation [9]. Our results are more in line with clinical trials of anticoagulant treatment for first-time cancer-associated venous thrombosis, demonstrating risks of 4%–9% in the initial six months, decreasing to <5% in the 6–12 month follow-up period [7–10].

Similar to the previous studies, we also report an initial high recurrence risk during the first six months, leveling out during the subsequent six months to one year.

Risk stratification tools for recurrent cancer-associated thrombosis, such as the Ottawa score, have failed to predict recurrent events in validation studies [27–29], and no prediction tool for recurrence is implemented in clinical guidelines [30,31]. We similarly did not report a consistent association between Ottawa risk score levels and recurrence risk, underlining the need for development of refined risk scores to aid clinical decision-making [21].

4.1. Strengths and limitations

Our study has several strengths. We used nationwide administrative and medical registries covering the complete Danish population. Data in the Danish Cancer Registry has compulsory reporting of malignancies, and most tumors have been histologically confirmed since 2009 [13]. All Danish hospitals and clinics report data on diagnoses including venous thromboembolism in the Danish National Patient Registry [14]. The register-based study design allowed for virtually complete follow-up of all study participants. The positive predictive value of venous thrombosis recorded in the Danish National Patient Registry overall has been shown to be >90% in conjunction with an imaging procedure, but the positive predictive value for recurrence among cancer patients is unknown [20,32]. Further, we restricted the recurrent diagnoses to those recorded >10 days apart from the incident diagnosis in alignment with previous studies [19], to limit inclusion of re-coded primary venous thromboembolic events as recurrent events.

Our study also has limitations. The datasets did not include information on socio-cultural determinants of health including race/ethnicity and lifestyle. However, all Danish inhabitants have tax funded access to health care services free of additional charge, and Denmark comprise a highly homogenous population. We did not have complete information on cancer stage for all patients, and on cancer progression during follow-up, and we were not able to differentiate catheter-related thrombosis from other VTEs. Low molecular weight heparin is used for treatment of cancer-associated thrombosis in Denmark and guidelines have recommend anticoagulant therapy for at least six months [22]. However, low molecular weight heparin is under-recorded in the Danish registries and thus we did not have complete information on initiation and duration of anticoagulant therapy. We also lacked information on site of first-time deep venous thrombosis, and on whether a proportion of venous thromboembolisms was incidentally diagnosed, for example during routine scans for cancer, which may also affect patients differently across age and cancer stage. Diagnosis of incidental pulmonary embolism without symptoms has been associated with a 30-day mortality of 3% compared with 21% among patients diagnosed with symptoms [33]. Similarly, a lower six months recurrence rate has been demonstrated in cancer patients with first-time incidental versus symptomatic venous thromboembolism (relative risk = 0.62) with no difference in overall mortality [34].

Autopsy studies have found underreporting of deaths from pulmonary embolism [35,36]. Underreporting could have resulted in underestimation of the recurrence risk in the current study, just as physicians in some cases may have forgotten to register a diagnosis of venous thromboembolism, thus limiting the sensitivity of using ICD codes to identify events.

5. Conclusion

The current study contributes with population-based data on recurrent cancer-associated venous thromboembolism, which remains a frequent complication in cancer patients, despite treatment

recommendations with anticoagulants for at least six months. Refining risk stratification for recurrence may improve decision-making regarding treatment duration after cancer-associated thromboembolism and ultimately lead to improvements in the net clinical benefit from anticoagulant treatment in this challenging patient population.

Funding information

This work was supported by the Danish Comprehensive Cancer Center. Professor Simon Noble's academic chair is funded by Marie Curie.

The funding source played no role in study design; the collection, analysis, or interpretation of data; or in the decision to submit the article for publication.

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Anne Gulbech Ording: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Project administration. **Peter Brønnum Nielsen:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Flemming Skjøth:** Conceptualization, Methodology, Investigation, Data curation, Resources, Formal analysis, Software, Validation, Visualization, Writing – review & editing. **Thure Filskov Overvad:** Conceptualization, Methodology, Writing – review & editing. **Simon Noble:** Conceptualization, Investigation, Writing – review & editing. **Timothy L. Lash:** Conceptualization, Investigation, Writing – review & editing. **Samuel Zachery Goldhaber:** Conceptualization, Investigation, Writing – review & editing. **Thomas Decker Christensen:** Conceptualization, Investigation, Writing – review & editing. **Torben Bjerregaard Larsen:** Conceptualization, Investigation, Resources, Writing – review & editing. **Mette Søgaard:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

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 and has been in an Advisory Board for Bayer, Merck Sharp & Dohme (MSD) and AstraZeneca. Torben Bjerregaard Larsen has been a speaker for Bayer, BMS/Pfizer, Janssen Pharmaceuticals, and Roche Diagnostics, and on an advisory board for Bayer, Bristol Meyers Squibb and Roche Diagnostics. Mette Søgaard has received consulting and speaker fees from Bayer. The other authors have nothing to declare.

Acknowledgement

The Danish Health Data authority provided the data for this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131271.

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