Risk of Depression after Venous Thromboembolism in Patients with Hematological Cancer: A Population-Based Cohort Study

Daniel Steiner[1,2] Erzsébet Horváth-Puhó[2] Helle Jørgensen[3] Kristina Laugesen[2,4] Cihan Ay[1] Henrik Toft Sørensen[2]

[1] Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Medical University of Vienna, Vienna, Austria
[2] Department of Clinical Epidemiology, Aarhus University Hospital and Aarhus University, Aarhus, Denmark
[3] Department of Clinical Medicine, Thrombosis Research Center (TREC), UiT–The Arctic University of Norway, Tromsø, Norway
[4] Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark

Address for correspondence Daniel Steiner, MD, Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria (e-mail: daniel.steiner@meduniwien.ac.at).

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Abstract

Background Venous thromboembolism (VTE) may complicate the clinical course of cancer patients and add to their psychological burden.

Objectives We aimed to investigate the association between VTE and risk of subsequent depression in patients with hematological cancer.

Patients and Methods We conducted a population-based cohort study using Danish national health registries. Between 1995 and 2020, we identified 1,190 patients with hematological cancer and incident VTE diagnosed within 6 months before to 1 year after cancer diagnosis. A comparison cohort of patients with hematological cancer without VTE ($n = 5{,}325$) was matched by sex, year of birth, cancer type, and year of cancer diagnosis. Patients were followed until diagnosis of depression, emigration, death, study end (2021), or for a maximum of 3 years. Depression was defined as hospital discharge diagnosis of depression or $\geq$1 prescription for antidepressants. Absolute risks of depression were computed with cumulative incidence functions, treating death as competing event. Hazard ratios (HRs) with 95% confidence intervals (CIs) were computed using Cox proportional hazards regression models, adjusting for comorbidities.

Results Depression was observed in 158 hematological cancer patients with and 585 without VTE. The 3-year absolute risks of depression were 13.3% (95% CI: 11.5–15.3%) in the VTE cancer cohort and 11.1% (95% CI: 10.3–12.0%) in the comparison cancer cohort, corresponding to a risk difference of 2.2% (95% CI: -1.8–6.5%). VTE was associated with an increased relative risk of depression (adjusted HR: 1.56, 95% CI: 1.28–1.90).

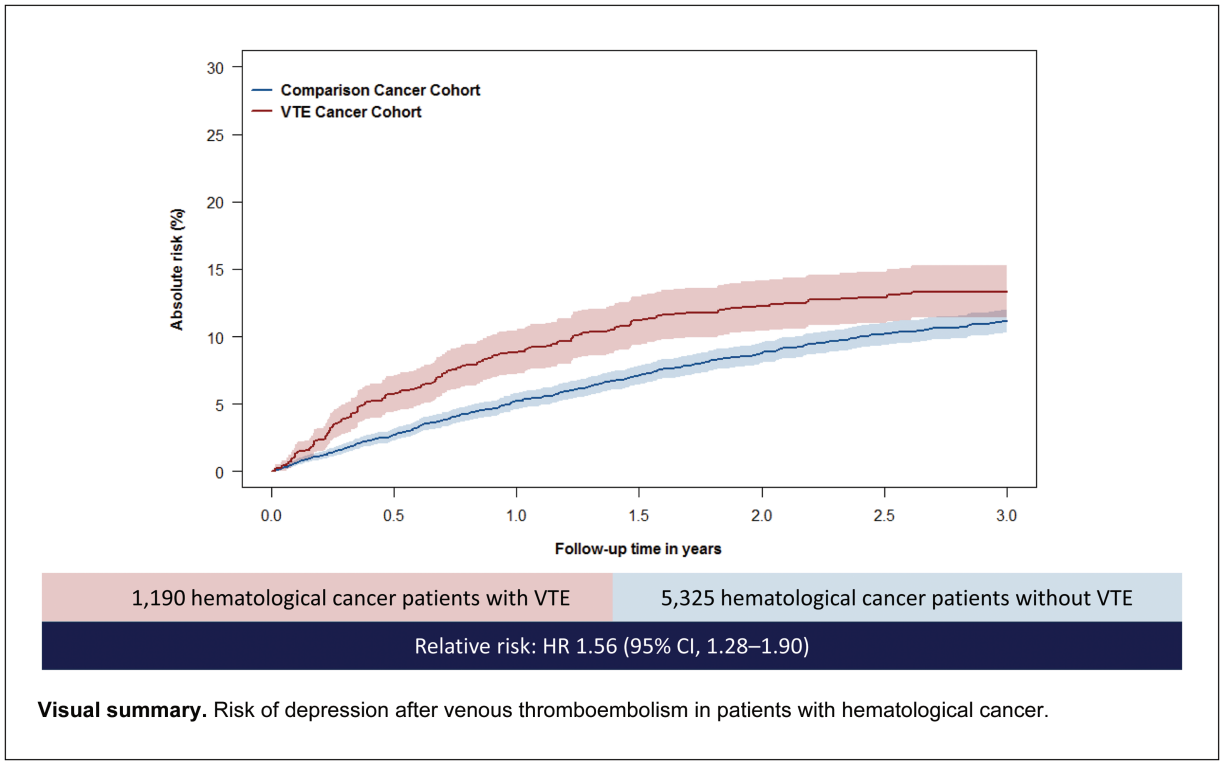
Conclusion VTE was associated with an elevated risk of subsequent depression in patients with hematological cancer.

Keywords
- epidemiology
- hematological cancer
- neoplasms
- disorders
- venous thromboembolism

received
October 6, 2023
accepted after revision
December 8, 2023
accepted manuscript online
December 11, 2023

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/a-2225-5428.
ISSN 0340-6245.



Visual summary. Risk of depression after venous thromboembolism in patients with hematological cancer.

Introduction

Patients with hematological cancer account for approximately 7% of all patients with cancer.[1] During recent decades, long-term survival in this cancer population has increased across various subtypes.[2] Nevertheless, this patient population represents a vulnerable group at risk of disease- and therapy-associated complications, including venous thromboembolism (VTE) and mental health disorders.[3–5]

VTE, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and severe complication of cancer.[6] Compared with the general population, cancer patients have a ninefold increased 12-month risk of VTE after their cancer diagnosis.[7] In patients with hematological cancer, the 10-year absolute risk of VTE has been reported to be approximately 5%.[3] Cancer-associated VTE affects the clinical course of the cancer, increases morbidity and mortality, and inflates health care costs, placing a substantial burden on both patients and the health care system.[8] The estimated point prevalence of depression 6 months after a hematological cancer diagnosis is approximately 17%.[5] Further, evidence from qualitative studies has suggested that cancer patients who suffer from a VTE perceive this event as a distressing experience that adds to the burden of cancer.[9–15] An association between VTE and mental health disorders in patients with cancer has only been reported in subgroup analyses of a few studies.[16,17] However, specific studies in patients with active cancer are lacking. Experiencing a VTE adds an additional layer of complexity to the care of patients with active hematological cancer and mental health complications in these patients remain poorly understood.[18]

Our aim, therefore, was to investigate the association between cancer-associated VTE and subsequent depression in patients with hematological cancer, using Danish population-based health registries.

Methods

Setting, Design, and Data Sources

Danish residents have free access to a universal tax-supported health care system.[19] At birth or immigration, all residents are assigned a unique civil personal registration number that enables unambiguous individual-level data linkage across Danish administrative and medical registries.[20] In our nationwide population-based cohort study, we used data collected prospectively during the period January 1, 1995 to December 31, 2021 from five Danish longitudinal health registries. Information on age, sex, date of migration, and death was obtained from the Danish Civil Registration System.[20] This administrative registry was established in 1968 and provides daily updates on vital status and migration of all persons residing in Denmark. Data on cancer diagnoses, cancer types, and cancer stages were extracted from the Danish Cancer Registry.[21,22] This registry records all incident cases of malignant neoplasms, including information on histology, morphology, and cancer stage. All cases are coded according to the *International Classification of Diseases, Seventh Revision* until 1978 and according to the *Tenth Revision* (ICD 10) from 1979 onward. Information on VTE, comorbidities, and discharge

diagnoses of depression was obtained from the Danish National Patient Registry (DNPR), covering all hospitals, and the Danish Psychiatric Central Research Register (DPCRR).[23,24] The DNPR contains hospital inpatient data since 1977 and emergency/outpatient clinic data since 1995. Each hospital discharge or outpatient clinic visit is recorded with one primary diagnosis and one or more secondary diagnoses classified according to the *International Classification of Diseases, Eighth Revision* (ICD-8) through 1993 and ICD-10 thereafter. The DPCRR has covered all psychiatric departments in Denmark since 1970. In 1995, outpatient clinic and emergency room data were added and the DPCRR became an integrated part of the DNPR. Information on redeemed prescriptions for antidepressants was extracted from the Danish National Prescription Registry.[25] This registry has covered all Danish pharmacies since 1995. Prescription drugs in the Danish National Prescription Registry are coded using the Anatomical Therapeutic Chemical coding system.

Venous Thromboembolism Cancer Cohort and Comparison Cancer Cohort

We identified patients ≥16 years of age diagnosed with hematological cancer and incident VTE between January 1, 1995 and December 31, 2020. Hematological cancers included Hodgkin malignant lymphoma, non-Hodgkin lymphoma, acute myeloid leukemia, acute lymphatic leukemia, chronic myeloid leukemia, chronic lymphatic leukemia, other leukemias, and multiple myeloma. Incident VTE was defined as an inpatient or outpatient, primary or secondary diagnosis of PE, DVT, or other VTE, excluding superficial thrombophlebitis, occurring within 6 months before to 1 year after the cancer diagnosis date (►**Supplementary Table S1**, available in the online version).[7] Patients with simultaneous PE and DVT were classified as having PE. Validity and completeness of cancer diagnoses in the Danish Cancer Registry are high, with 89% of tumors morphologically verified.[22] The validity of VTE diagnoses in the DNPR has been examined previously, with positive predictive values ranging from 80 to 90%, and negative predictive values exceeding 99%.[26,27]

For each member of the VTE cancer cohort, we randomly sampled up to five individuals from a population of patients with hematological cancer but without VTE, with replacement.[28] The comparison cancer cohort was matched by sex, year of birth (in 2-year intervals), type of cancer, and year of cancer diagnosis (in 2-year intervals). The index date of comparison cancer cohort members was set as the VTE diagnosis date of the matched member of the VTE cancer cohort. Individuals in the comparison cancer cohort experiencing a VTE event during follow-up were censored at the time of their VTE diagnosis. Patients with a diagnosis of depression or a redeemed prescription for antidepressants before the index date were not included in the study.

Depression

We defined depression as an inpatient or outpatient specialist clinic diagnosis of depression or a minimum of one redeemed prescription for an antidepressant (►**Supplementary Table S1**, available in the online version). The validity of a depressive episode recorded in the DPCRR has been examined previously, with positive predictive values ranging between 65% for mild depression and 83% for severe depression.[29] We included data on redeemed prescriptions for antidepressants in our depression definition, since many patients with depression are managed by general practitioners, and data from the general practice setting are not included in the DNPR or the DPCRR.[23]

Covariates

The following comorbidities, measured at any time before the VTE diagnosis/index date, were considered potential confounding factors (►**Supplementary Table S1**, available in the online version): heart disease (including coronary artery disease, atrial fibrillation/flutter, heart failure, and cardiomyopathy), chronic pulmonary disease (including chronic obstructive pulmonary disease, asthma, and interstitial lung diseases), diabetes mellitus types I and II, acute kidney failure, chronic kidney disease, liver disease, obesity, stroke, inflammatory bowel disease, hypertension, mental health disorders other than depression, surgery (3 months before the VTE diagnosis or index date), and trauma/fracture (3 months before the VTE diagnosis or index date). For patients with lymphoma, cancer stage also was considered a covariate.

Statistical Analysis

We characterized the study cohorts according to sex, age group, calendar period of the index date, VTE type, cancer type, and comorbidities.

The study cohorts were followed from the index date until the first occurrence of depression, emigration, death, study end (December 31, 2021), or for a maximum of 3 years. Absolute risks and risk differences of depression in the VTE cancer cohort and the comparison cancer cohort were computed using cumulative incidence functions, treating death as a competing event.[30] Stratified Cox proportional hazard regression models were used to compute unadjusted and adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Unadjusted HRs were controlled for matching variables through the study design, while adjusted HRs were adjusted for the potential confounding factors listed above (►**Supplementary Table S1**, available in the online version). Log-minus-log plots were created and indicated no major violation of the proportional-hazards assumption. Analyses were stratified by sex, age groups (16–44 years, 45–64 years, and 65+ years, corresponding to early to middle working age, late working age, and retirement age, respectively), and type of VTE event (PE, DVT, or other VTE). Analyses stratified by cancer type were performed for the predefined cancer subtypes described above, whenever the sample size was sufficient. In the analysis of non-Hodgkin lymphoma patients, we adjusted for local, regional, distant, or missing cancer stage. Furthermore, we performed a stage-stratified analysis of non-Hodgkin lymphoma patients. Finally, we performed a time-restricted analysis with a maximum of 1 year of follow-up to investigate the temporal effects of the occurrence of depression.

To evaluate the robustness of our main results, we performed several sensitivity analyses. First, as antidepressants

might be prescribed for conditions other than depression, we restricted the outcome definition to hospital diagnoses of depression. Second, to avoid informative censoring, we performed an analysis in which the comparison cohort members experiencing a VTE event during follow-up were not censored at the time of VTE diagnosis, thereby mimicking an intention-to-treat analysis.[28]

All analyses were conducted using SAS version 9.4 (SAS Institute, INC, Cary, North Carolina, United States). The study was reported to the Danish Data Protection Agency (record number 2016–051–000001–812). The study followed the reporting guidelines recommended by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[31]

Results

Characteristics of the Study Cohorts

A total of 1,190 patients were included in the VTE cancer cohort, and 5,325 patients were included in the comparison cancer cohort. Characteristics of the two cohorts are presented in ►**Table 1**. Approximately half of all patients in the two cohorts had non-Hodgkin lymphoma, and approximately 20% had multiple myeloma. Comorbidities were generally well balanced between cohorts. However, more patients in the VTE cancer cohort had surgery 3 months before the VTE diagnosis date (►**Table 1**). The 3-year mortality risks were 43.5% (95% CI: 40.8–46.4%) in the VTE cancer cohort and 28.2% (95% CI: 26.9–29.4%) in the comparison cancer cohort (►**Supplementary Fig. S1**, available in the online version). Median follow-up times were 2.3 and 3.0 years, respectively.

Absolute Risks and Hazard Ratios of Depression

After 3 years, depression was observed in 158 patients in the VTE cancer cohort and 585 patients in the comparison cancer cohort. The absolute 3-year risks of depression were 13.3% (95% CI: 11.5–15.3%) and 11.1% (95% CI: 10.3–12.0%) in the VTE cancer cohort and the comparison cancer cohort, respectively, corresponding to a risk difference of 2.2% (95% CI: −1.8% to 6.5%) (►**Fig. 1** and ►**Table 2**). The association between cancer-associated VTE and depression showed a temporal pattern, with a steep increase in the absolute risk during the first 1.5 years of follow-up and a subsequent convergence in the following months (►**Fig. 1**). VTE in cancer patients was associated with an increased relative risk of depression (adjusted HR: 1.56 [95% CI: 1.28–1.90]) (►**Table 2**). When follow-up time was restricted to a maximum of 1 year, the absolute risk of depression in the VTE cancer cohort was 8.8% (95% CI: 7.3–10.5%) compared with 5.2% (95% CI: 4.6–5.8%) in the comparison cancer cohort, corresponding to a risk difference of 3.6% (95% CI: 0.4–7.1%) (►**Fig. 1** and ►**Table 2**). The adjusted HR after 1 year of follow-up was 2.04 (95% CI: 1.59–2.62) (►**Table 2**).

Analyses Stratified by Sex, Age Groups, and Type of Venous Thromboembolism Event

Estimates stratified by sex, age group, and type of VTE are shown in ►**Table 2**. The absolute 3-year risks of depression in women were 16.1% (95% CI: 12.9–19.5%) in the VTE cancer cohort and 12.2% (95% CI: 10.8–13.6%) in the comparison cancer cohort. The absolute risks in men were 11.5% (95% CI: 9.3–14.0%) and 10.4% (95% CI: 9.4–11.5%), respectively. The adjusted HRs for women and men were 1.64 (95% CI: 1.23–2.20) and 1.50 (95% CI: 1.14–1.96), respectively. The absolute 3-year risks stratified by age groups in the VTE cancer and comparison cancer cohorts are shown in ►**Table 2**. Patients of early to middle working age showed the strongest association between VTE and depression, but with the lowest precision (adjusted HR: 1.87 [95% CI: 0.86–4.08]). Adjusted HRs for patients of late working age and retirement age were 1.75 (95% CI: 1.23–2.48) and 1.45 (95% CI: 1.12–1.87), respectively. When stratifying patients by type of VTE event, the absolute 3-year risks of depression after PE were 13.5% (95% CI: 10.6–16.8%) in the VTE cancer cohort and 11.8% (95% CI: 10.4–13.2%) in the comparison cancer cohort. The absolute risks after DVT were 14.0% (95% CI: 11.0–17.3%) and 11.0% (95% CI: 9.7–12.4%), respectively. The absolute risks after other VTE were 11.9% (95% CI: 8.3–16.1%) and 10.1% (95% CI: 8.4–12.0%), respectively. The strongest association was observed in patients with PE (adjusted HR: 1.77 [95% CI: 1.30–2.41]), compared with patients with DVT (adjusted HR: 1.35 [95% CI: 0.99–1.85]) and with other VTE (adjusted HR: 1.52 [95% CI: 0.94–2.44]).

Analyses Stratified by Type of Cancer

Subgroup analyses were only performed in patients with non-Hodgkin lymphoma and multiple myeloma, as cohort sizes were too small for other cancer types. The absolute 3-year risks of depression in patients with non-Hodgkin lymphoma were 11.1% (95% CI: 8.8–13.8%) in the VTE cancer cohort and 9.7% (95% CI: 8.6–10.8%) in the comparison cancer cohort (►**Supplementary Table S2**, available in the online version). The adjusted HR was 1.51 (95% CI: 1.12–2.04) (►**Supplementary Table S2**, available in the online version). Absolute 3-year risks of depression in stage-stratified analyses of patients with non-Hodgkin lymphoma are shown in ►**Table 3**. The association between VTE and depression was stronger in patients with distant stage disease than in patients with regional and localized stage (adjusted HRs [95% CI]: 1.88 [1.20–2.93], 1.62 [0.82–3.18], and 1.32 [0.61–2.88], respectively). In patients with multiple myeloma, the absolute 3-year risks of depression were 18.3% (95% CI: 13.7–23.5%) in the VTE cancer cohort and 17.1% (95% CI: 15.0–19.4%) in the comparison cancer cohort. The corresponding adjusted HR was 1.39 (95% CI: 0.97–1.98) (►**Supplementary Table S2**, available in the online version).

Sensitivity Analyses

In the sensitivity analysis in which the outcome was restricted to hospital diagnoses of depression, the absolute risks were 1.0% (95% CI: 0.6–1.7%) in the VTE cancer cohort and 0.6% (95% CI: 0.4–0.8%) in the comparison cancer cohort, corresponding to a risk difference of 0.5% (95% CI: −0.6 to 1.9). The adjusted HR was 1.98 (95% CI: 0.90–4.37). In the sensitivity analysis in which individuals in the comparison cancer cohort experiencing a VTE event during follow-up

Table 1 Demographics and clinical characteristics of the venous thromboembolism cancer cohort and the comparison cancer cohort, Denmark, 1995–2020

	VTE cancer cohort ($n = 1,190$), *n* (%)	Comparison cancer cohort ($n = 5,325$), *n* (%)
Female	481 (40.4)	2,104 (39.5)
Age, median (interquartile range)	68.6 (58.8–76.8)	69.3 (60.5–76.9)
Age group		
16–34	51 (4.3)	154 (2.9)
35–44	57 (4.8)	193 (3.6)
45–54	104 (8.7)	395 (7.4)
55–64	251 (21.1)	1,181 (22.2)
65–79	536 (45.0)	2,548 (47.8)
80+	191 (16.1)	854 (16.0)
Type of VTE		
Pulmonary embolism	475 (39.9)	–
Deep vein thrombosis	453 (38.1)	–
Other VTE[a]	262 (22.0)	–
Cancer type		
Hodgkin malignant lymphoma	81 (6.8)	264 (5.0)
Non-Hodgkin lymphoma	595 (50.0)	2,915 (54.7)
Acute myeloid leukemia	94 (7.9)	312 (5.9)
Acute lymphatic leukemia	20 (1.7)	31 (0.6)
Chronic myeloid leukemia	13 (1.1)	26 (0.5)
Chronic lymphatic leukemia	119 (10.0)	561 (10.5)
Other leukemia	26 (2.2)	73 (1.4)
Multiple myeloma	242 (20.3)	1,143 (21.5)
Year of VTE diagnosis/index date		
1995–1999	105 (8.8)	477 (9.0)
2000–2004	189 (15.9)	838 (15.7)
2005–2009	207 (17.4)	913 (17.1)
2010–2014	331 (27.8)	1,426 (26.8)
2015–2020	358 (30.1)	1,671 (31.4)
Comorbidities		
Cardiovascular disease[b]	206 (17.3)	934 (17.5)
Chronic pulmonary disease[c]	92 (7.7)	357 (6.7)
Diabetes mellitus, type I or II	79 (6.6)	341 (6.4)
Acute kidney failure and chronic kidney disease	65 (5.5)	203 (3.8)
Liver disease	23 (1.9)	82 (1.5)
Obesity	50 (4.2)	156 (2.9)
Stroke (hemorrhagic or ischemic)	43 (3.6)	190 (3.6)
Inflammatory bowel disease	32 (2.7)	114 (2.1)
Hypertension	237 (19.9)	921 (17.3)
Mental health disorders other than depression	52 (4.4)	224 (4.2)
Surgery 3 months before VTE/index date	321 (27.0)	597 (11.2)
Trauma/fracture 3 months before VTE/index date	29 (2.4)	73 (1.4)

(*Continued*)

Table 1 (*Continued*)

	VTE cancer cohort ($n = 1{,}190$), *n* (%)	Comparison cancer cohort ($n = 5{,}325$), *n* (%)
Modified CCI score[d]		
Score 0	794 (66.7)	3,597 (67.5)
Score: 1	206 (17.3)	1,047 (19.7)
Score: 2	116 (9.7)	424 (8.0)
Score: 3+	74 (6.2)	257 (4.8)

Abbreviations: CCI, Charlson comorbidity index; VTE, venous thromboembolism.
Values are presented as numbers (and percentages) unless otherwise stated.
[a]Including portal vein thrombosis, VTE of unspecified site, pregnancy-related VTE, and nonpyogenic thrombosis of the intracranial venous system.
[b]Including coronary artery disease, atrial fibrillation/flutter, heart failure, and cardiomyopathy.
[c]Including COPD, asthma, and interstitial lung diseases.
[d]Excluding cancer-associated diagnoses.

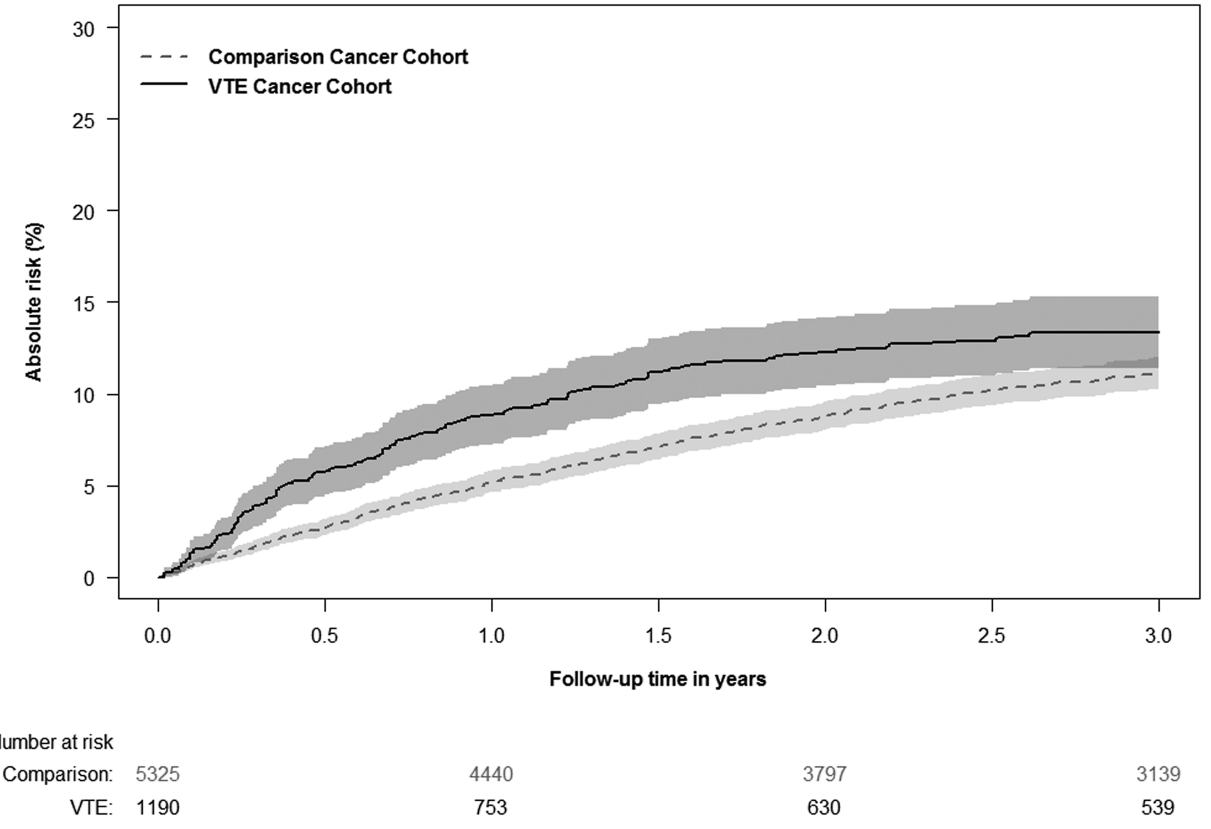


Fig. 1 Absolute risk (%) of subsequent depression in patients with hematological cancer with or without venous thromboembolism. Absolute risk of patients with VTE is depicted with a solid line (VTE cancer cohort) and absolute risk of patients without VTE with a dashed line (comparison cancer cohort). Death was treated as a competing event. VTE, venous thromboembolism.

were not censored at the time of VTE diagnosis, the estimates remained largely unchanged (►**Supplementary Table S3**, available in the online version).

Discussion

In this nationwide population-based cohort study, patients with hematological cancer and VTE were found to be at increased risk of subsequent depression compared with patients with hematological cancer without VTE. The association was strongest in patients with PE, in patients with distant-stage non-Hodgkin lymphoma, and during the first year after the VTE.

The association between overall VTE and depression or other psychiatric disorders in the general population has been reported in two large-scale studies.[16,17] In a Danish nationwide population-based cohort study of 64,596 individuals with VTE, the absolute risk of depression after 3 years was found to be 10.3%, compared with 5.6% in the general

Table 2 Absolute risks (%) and hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) of depression among patients with hematological cancer with or without venous thromboembolism

	Comparison cancer cohort ($n = 5,325$)			VTE cancer cohort ($n = 1,190$)				
	Number at risk	Events	Absolute risk (%) (95% CI)	Number at risk	Events	Absolute risk (%) (95% CI)	Model 1 Unadjusted HR (95% CI)	Model 2 Adjusted HR (95% CI)
Full cohort	5,325	585	11.1 (10.3–12.0)	1,190	158	13.3 (11.5–15.3)	1.55 (1.28–1.87)	1.56 (1.28–1.90)
Full cohort, follow-up restricted to 1 year	5,325	277	5.2 (4.6–5.8)	1,190	105	8.8 (7.3–10.5)	2.09 (1.65–2.66)	2.04 (1.59–2.62)
Women	2,104	254	12.2 (10.8–13.6)	481	77	16.1 (12.9–19.5)	1.74 (1.32–2.31)	1.64 (1.23–2.20)
Men	3,221	331	10.4 (9.4–11.5)	709	81	11.5 (9.3–14.0)	1.40 (1.08–1.82)	1.50 (1.14–1.96)
Age: 16–44	347	32	9.4 (6.6–12.8)	108	14	13.1 (7.5–20.2)	1.74 (0.86–3.52)	1.87 (0.86–4.08)
Age: 45–64	1,576	171	11.0 (9.5–12.6)	355	57	16.2 (12.5–20.2)	1.80 (1.30–2.51)	1.75 (1.23–2.48)
Age: 65+	3,402	382	11.4 (10.3–12.5)	727	87	12.0 (9.8–14.5)	1.43 (1.11–1.83)	1.45 (1.12–1.87)
PE	2,138	247	11.8 (10.4–13.2)	475	64	13.5 (10.6–16.8)	1.73 (1.29–2.33)	1.77 (1.30–2.41)
DVT	2,058	225	11.0 (9.7–12.4)	453	63	14.0 (11.0–17.3)	1.40 (1.04–1.90)	1.35 (0.99–1.85)
Other VTE	1,129	113	10.1 (8.4–12.0)	262	31	11.9 (8.3–16.1)	1.51 (0.99–2.31)	1.52 (0.94–2.44)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.
Note: Model 1: unadjusted model controlling for matching variables by study design. Model 2: adjusted for cardiac disease (including coronary artery disease, atrial fibrillation/flutter, heart failure, and cardiomyopathy), chronic pulmonary disease (including COPD, asthma, and interstitial lung diseases), diabetes mellitus types I and II, acute kidney failure and chronic kidney disease, liver disease, obesity, hemorrhagic and ischemic stroke, inflammatory bowel disease, hypertension, any mental health disorder, surgery 3 months before the VTE diagnosis or index date, and trauma/fracture 3 months before the VTE diagnosis or index date.

Table 3 Absolute risks (%) and hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) of depression among patients with non-Hodgkin lymphoma with or without venous thromboembolism, stratified by cancer stage

	Non-Hodgkin lymphoma without VTE ($n = 2{,}915$)[a]			Non-Hodgkin lymphoma with VTE ($n = 595$)[a]				
Cancer stage	Number at risk	Events	Absolute risk (%) (95% CI)	Number at risk	Events	Absolute risk (%) (95% CI)	Model 1 Unadjusted HR (95% CI)	Model 2 Adjusted HR (95% CI)
Localized	519	47	9.1 (6.8–11.8)	68	8	11.8 (5.5–20.7)	1.48 (0.70–3.13)	1.32 (0.61–2.88)
Regional	531	44	8.3 (6.2–10.9)	123	11	8.9 (4.7–14.8)	1.22 (0.63–2.37)	1.62 (0.82–3.18)
Distant	813	75	9.3 (7.4–11.5)	214	29	13.6 (9.4–18.6)	1.98 (1.29–3.05)	1.88 (1.20–2.93)

Abbreviation: VTE, venous thromboembolism.

Note: Model 1: unadjusted model controlling for matching variables by study design. Model 2: adjusted for cardiac disease (including coronary artery disease, atrial fibrillation/flutter, heart failure, and cardiomyopathy), chronic pulmonary disease (including COPD, asthma, and interstitial lung diseases), diabetes mellitus types I and II, acute kidney failure and chronic kidney disease, liver disease, obesity, hemorrhagic and ischemic stroke, inflammatory bowel disease, hypertension, any mental health disorder, surgery 3 months before the VTE diagnosis or index date, and trauma/fracture 3 months before the VTE diagnosis or index date.

[a]Staging was not available for 1,052 (36.1%) patients in the non-Hodgkin lymphoma group without VTE and 190 (31.9%) patients in the non-Hodgkin lymphoma group with VTE; therefore, these patients are excluded from the analysis.

population.[16] In a subgroup analysis of individuals with VTE and cancer, the incidence rate of depression was almost 100 events per 1,000 person-years and the adjusted HR was 2.96 (95% CI: 2.58–3.41).[16] A nationwide cohort study from Taiwan investigating the risk of psychiatric disorders in 21,916 patients with PE and a sex- and age-matched comparison cohort found that PE was associated with a twofold increased risk of depression (adjusted HR: 2.04, 95% CI: 1.72–2.39).[17] In a subgroup analysis stratified by the presence of cancer, the incidence rates of any psychiatric disorder in cancer patients with or without PE were 20.0 and 4.2 per 1,000 person-years, respectively.[17] However, patients with cancer in these two studies were defined as having any cancer diagnosis before or on the VTE diagnosis date, not necessarily indicating a temporal link between cancer and VTE.[16,17] Further, the comparison cohorts were sampled from the general population, making a direct comparison to the current study difficult.

Evidence from qualitative studies suggests that patients with cancer experience VTE as an unexpected and frightening burden on top of the difficulties facing them due to cancer.[15] Our findings confirm quantitative results from the general population and qualitative evidence from the cancer population.[15–17] Compared with the general population,[16] both the VTE cancer cohort and the comparison cancer cohort had higher absolute risks of depression in our study. This might be explained by the association between cancer and depression.[5] Conversely, the additional effect of VTE on the occurrence of subsequent depression in cancer patients seems to be smaller than in the general population.[16] When investigating temporal trends, the association between VTE and subsequent depression in our study was particularly strong during the first year after VTE diagnosis. This suggests that VTE has an acute rather than chronic impact on mental health. Psychological effects of VTE might subside over time and other factors influencing mental health might come into play. Importantly, the observed association was not attenuated after adjusting for potential confounders. Therefore, it is less likely that the occurrence of depression in patients with VTE was merely a representation of their poorer overall health. While the stratified analyses in our study were limited by the small cohort size, we nevertheless observed a stronger association between cancer-associated PE and subsequent depression compared with DVT, which is in line with data from the general population.[16] Further, we performed stage-stratified analyses in non-Hodgkin lymphoma patients, showing a strong association between VTE and subsequent depression in patients with distant-stage disease.

We focused on patients with hematological cancers in our study. Cancer surgery, which is a potential link between cancer and depression, is not frequently performed in hematological cancer patients.[32] However, hematological cancers encompass a wide range of cancer types whose VTE risk varies not only by the type and subtype of cancer but also by cancer-specific therapies and interventions.[33] In particular, the 1-year VTE incidence of non-Hodgkin lymphoma might range from 1.4% in indolent lymphomas up to 4.3% in

peripheral T cell lymphomas.[34] Furthermore, cancer stage has been shown to be associated with VTE in solid malignancies.[7] Therefore, cancer type and cancer stage might be considered as part of the exposure, potential confounders, or mediators in the association between cancer-associated VTE and depression. We performed several approaches to evaluate these potential effects. First, we matched patients by cancer type and year of cancer diagnosis to attenuate the influence of cancer type-specific VTE risk, treatment patterns, and prognosis. Second, we adjusted for cancer stage in the stratified analysis of non-Hodgkin lymphoma patients, which did not affect the association. Furthermore, we performed a stage-stratified analysis in non-Hodgkin lymphoma patients, which showed a particularly strong association with distant-stage disease, thus making it less likely that cancer stage acts as a strong confounder in these patients.

Our study has several strengths and limitations. First, it was conducted in a setting with universal health care provided free of charge, thereby reducing the risk of selection and referral biases. Our data sources have been shown to be complete and accurate, with high positive predictive values for both VTE and cancer diagnoses.[21,22,26,27] The positive predictive values for depression in the utilized data sources range between 65% for mild depression and 83% for severe depression.[29] To include mild cases of depression that often are treated in the primary care setting, and to increase data completeness, we defined our outcome as a combination of both depression diagnoses and redeemed prescriptions for antidepressants. As antidepressants could be prescribed for reasons other than depression, we performed a sensitivity analysis restricted to hospital diagnoses of depression. While the association persisted in the sensitivity analysis, the limited number of events reduced the statistical precision of the estimates. To investigate the effect of cancer-associated VTE on subsequent incident cases of depression, we did not include cancer patients who had been diagnosed with depression or who had been using antidepressants before the VTE. Nonetheless, these patients could be at great risk of experiencing a worsening of their pre-existing depression. As this study was restricted to hematological cancers, our findings may not be generalizable to other cancer types. Another potential concern might be that we cannot rule out differential misclassification bias related to greater contact with the health care system among patients with VTE compared to those without VTE.[35] However, patients in the comparison cancer cohort would be expected to have similar contact with the health care system because of their cancer diagnosis. Our stratified analyses had lower statistical precision due to the sample size. Finally, residual confounding due to unmeasured cancer-associated factors such as cancer therapies, peripheral and central catheters, infections, bleeding events, and lymphoma subtypes, e.g., aggressive or indolent lymphomas, cannot be completely ruled out.

In conclusion, this study found that VTE is associated with an increased risk of subsequent depression in patients with hematological cancer. The psychological effects of cancer-associated VTE call for strategies to identify and prevent depression in patients with hematological cancer and VTE.

What is known about this topic?

- Venous thromboembolism is associated with depression in the general population.
- In patients with cancer, venous thromboembolism is suggested to add a psychological burden, but dedicated studies in cancer-only populations are lacking.

What does this paper add?

- In patients with hematological cancer, venous thromboembolism is associated with an elevated risk of subsequent depression compared with patients without venous thromboembolism.
- This additional mental health burden calls for strategies to identify and prevent depression in patients with hematological cancer and venous thromboembolism.

Note

The Department of Clinical Epidemiology receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University (none of these studies has any relation to the present study).

Data Availability Statement

Individual-level patient data from this study cannot be made available to other researchers due to Danish privacy law, but can be obtained from the Danish Health Data Agency.

Authors' Contribution

D.S., E.H.-P., H.J., C.A., and H.T.S. contributed to study concept and design. E.H.-P. performed the statistical analysis. All authors contributed to interpretation of the data. D.S. drafted the manuscript. All authors critically revised the manuscript and approved the final version before submission.

Funding Sources

The work was supported by the Independent Research Fund Denmark (record no. 3101–00102B) and the Karen Elise Jensen's Foundation.

Conflict of Interest

C.A. reports honoraria for lectures from Bayer, Daiichi Sankyo, BMS/Pfizer, and Sanofi, and participation in advisory boards for Bayer, Boehringer Ingelheim, Daiichi Sankyo, and BMS/Pfizer (none of these have any relation to the present study). The remaining authors declare no competing financial interests.

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