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ORIGINAL ARTICLE

Cancer-associated venous thromboembolism in Israel: Incidence, risk factors, treatment, and health care utilization in a population based cohort study

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Abstract

Background: Recent international guidelines recommend thromboprophylaxis in patients with cancer at intermediate-high venous thromboembolism (VTE) risk.

Objectives: We aimed to assess the current incidence, risk factors and management of cancer-associated VTE and associated health care resource utilization in a 2.5-million-member state-mandated health service in Israel.

Methods: Patients aged ≥18 years with newly diagnosed cancer, initiating systemic anticancer treatment from 2010 through 2018 were identified from the Israel National Cancer Registry. The index date was fixed as the first day of systemic anticancer treatment. The cumulative VTE incidence from the first day of systemic anticancer treatment and the respective hazard ratios for VTE risk factors were calculated at 12 months of follow-up. Health care resource utilization (primary care physician, emergency room, and hospital visits) during the study period was compared between patients with and without VTE.

Results: A total of 15 388 patients were included, and 338 had VTE with a 12-month cumulative incidence of 2.2% (95% confidence interval, 1.96%-2.43%). In a multivariable model, older age, higher comorbidity index, intermediate-high-risk Khorana score, certain malignancy types, and chemotherapy were significantly associated with an increased VTE risk in the year after initiating anticancer treatment. Compared with matched controls, the VTE subcohort were more likely to be hospitalized (81.4% vs 35.2%), have longer hospital stays (20.1 days vs 13.1 days), have an emergency room visit (41.5% vs 19.3%), and have a larger number of primary care physician visits (17.6 vs 12.5).

Conclusion: Several risk factors, including the Khorana score, were associated with VTE incidence. VTE was associated with long-term use of anticoagulation. Health care utilization was higher in patients with VTE.

KEYWORDS
anticoagulation, cancer, health care resource utilization, risk assessment, venous thromboembolism

Essentials

- This was a population-based cohort study of adult patients with cancer receiving anticancer therapy (2010–2018).
- The 12-month cumulative incidence of venous thromboembolism (VTE) was 2.2% (1.96%-2.43%).
- Risk factors for VTE include age, higher-risk Khorana score, certain malignancy types, and chemotherapy.
- Health care resource utilization was higher for patients with VTE versus matched controls after VTE.

1 | INTRODUCTION

Malignant disease is associated with a hypercoagulable state that increases the risk of development of venous thromboembolism (VTE) by at least 4-fold,[1] particularly in the first year after cancer diagnosis.[2,3] Cancer-associated thrombosis (CAT)/VTE is associated with short- and long-term morbidity such as recurrent VTE and major bleeding,[4,5] significant health care resource utilization (HCRU), and increased all-cause costs among ambulatory patients with cancer.[5-7] In addition, CAT is associated with reduced survival compared to patients with cancer without VTE[8,9] and is the leading cause of death in patients with cancer receiving outpatient chemotherapy.[6]

The risk of developing CAT depends on numerous factors including age, lifestyle, ethnicity, type of malignancy, cancer stage, and cancer treatment,[1,8,10] with cancers such as pancreas, stomach, brain, and lung, and certain chemotherapeutic therapies associated with higher rates of CAT.[11-14] A number of prediction models have been developed to assess the risk of CAT in ambulatory cancer patients,[15-17] with the most extensively validated and utilized one being the Khorana score, which uses clinical (malignancy type, body mass index [BMI]) and laboratory parameters (hemoglobin, leukocytes, and platelet count) to stratify VTE risk. According to the original Khorana score classification, patients with low- (score = 0), intermediate- (1-2), and high-risk (≥3) Khorana score have corresponding 6-month VTE rates of 1.5%, 3.8% to 9.6%, and 17.7%, respectively.[18]

Thromboprophylaxis with low-molecular-weight heparin (LMWH) or direct oral anticoagulants (DOACs) has been shown to reduce VTE rates in ambulatory patients with cancer receiving chemotherapy.[16,19,20] A study with apixaban included patients with an intermediate- or high-risk Khorana score (≥2), and led to a more acceptable number needed to treat than studies using LMWH for unselected patients with cancer.[19] A similar study with rivaroxaban demonstrated a nonsignificant reduction in 6-month VTE incidence, in the primary analysis.[21] Consequently, recent international guidelines recommend VTE risk assessment for all outpatients with cancer and suggest considering thromboprophylaxis with LMWH or DOAC in patients with a Khorana score of ≥2 receiving chemotherapy for active cancer.[22-25] The American Society of Hematology guidelines suggest thromboprophylaxis with a DOAC for patients at intermediate risk of thrombosis, and LMWH or DOACs for those at high risk.[25] Once CAT is diagnosed, the American Society of Clinical Oncology and American College of Chest Physicians guidelines both suggest the use of LMWH or a DOAC in patients diagnosed with VTE and cancer for at least 3 to 6 months.[22,26] Since CAT is associated with higher health care costs and more hospital admissions compared to patients with cancer without VTE, thromboprophylaxis in ambulatory patients with cancer could theoretically reduce the burden associated with CAT, such as long-term use of anticoagulation and HCRU.[27-30]

This noninterventional observational study aimed to generate real-world data on the incidence and risk factors of CAT, current practice with regard to VTE treatment, and the burden of HCRU among patients with newly diagnosed cancer in Israel from January 2010 to December 2018.

2 | METHODS

2.1 | Data source

This population-based retrospective cohort study was conducted using the computerized databases of Maccabi Healthcare Services (MHS), a nationwide health care insurer-provider. MHS has ≈2.5 million members, representing a quarter of the Israeli population, and shares similar sociodemographic characteristics with the general population.[31] The MHS database contains longitudinal data that have been automatically collected since 1993 for a stable population (with <1% of members moving out each year), including laboratory results from a single central laboratory, pharmacy prescription and purchase data, hospitalizations, procedures, and consultations. MHS uses the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding systems for all diagnosis data, as well as self-developed coding systems to provide more granular diagnostic information. Procedures are coded using Current Procedural Terminology codes. MHS has developed several computerized registries of major chronic diseases, such as cardiovascular disease, oncologic diseases, diabetes mellitus, chronic kidney disease, and osteoporosis, to improve the quality of chronic care delivery to its members. The registries are continuously updated, and they identify patients via automatic search formulas, as opposed to being dependent upon active reporting by physicians.[32-34] By law, all pathology

results from diagnosed cancer cases must be submitted to the national register. The MHS cancer registry is compiled at the patient level from the national registry and linked to cancer treatment approvals by the MHS drug approval committee and cancer pathology reports.

2.2 | Study population

Patients aged ≥18 years between January 1, 2010, and December 31, 2018, with a first diagnosis of cancer from the MHS cancer registry were eligible for inclusion if they were newly diagnosed and newly treated (excluding basal cell or squamous cell skin carcinoma). First-line anticancer treatment was defined by a systemic anticancer drug purchase or a hospital request for payment for administration of chemotherapy. Exclusion criteria included patients with <1 year of health care registration in MHS before the index date, any superficial or deep vein thrombosis or pulmonary embolism event before the index date (using a validated algorithm[35] or VTE ICD-9-CM codes [see Supporting Information]), or anticoagulation purchase within 3 months before the index date. In addition, women with evidence of pregnancy from specific treatment codes (eg, ultrasound, amniocentesis) during the baseline year or index year were excluded.

The index date was set as the date of initiation of first-line systemic anticancer treatment. Data were collected until December 31, 2019, to allow at least 1 year of follow-up. Individuals were followed from index date until death, loss to follow-up, or end of study period, whichever occurred first.

2.3 | Study variables

Demographic and clinical data collected included age at index, sex, socioeconomic status, district, prevalence of comorbid conditions, BMI, and smoking status. Smoking data were collected from physician reporting and classified into ever, never, or unknown. BMI was defined as the closest to the index date within the 5-year period before the index date. (Median time from measurement of BMI to index date was less than half a year [165 days; interquartile range [IQR], 60-441] and there was <5% missing data). The Deyo-Charlson comorbidity index, using ICD-9-CM codes and MHS registries to determine presence/absence of disease, was calculated.[36] The definitions of socioeconomic status, comorbidities, Khorana score calculation, and major bleeding events (using validated ICD-9-CM algorithms) are detailed in the Supporting Information.

The modified Khorana score was used to stratify VTE risk at index as low (0-1) or intermediate-high (≥2) risk (representing intermediate- to high-risk scores), as in the trials assessing DOACs for prevention of CAT.[19,21] Cancer site was grouped as hematological, solid, or unknown and further classified into site of cancer (ie, digestive [any cancer in the gastrointestinal tract, including intestine, pancreas, and stomach], brain and nervous system, respiratory, breast, and other). First line anticancer treatment was classified from purchase data as chemotherapy (with or without monoclonal antibodies [which includes immunotherapy]), hormonal treatment, monoclonal antibodies, targeted treatment (protein kinase inhibitors), and unknown. Drug purchases before index date (purchased within 3 months' before index) were collected for estrogen-containing therapy. Patients who received prophylaxis anticoagulation treatment were defined as those who received anticoagulation after the index date and before VTE diagnosis date (as defined from the VTE algorithm) or those with no VTE event.

2.4 | Outcomes

The main outcome was the first VTE event (deep vein thrombosis or pulmonary embolism), identified using a validated algorithm based on diagnostic codes and anticoagulation prescription data for the 1-year period following the index date.[35] Diagnosis codes were captured from inpatient and outpatient data. Diagnosis from inpatient data was assigned a VTE diagnosis on the last date of hospitalization.

Patients who experienced a VTE during the 1-year follow-up (ie, VTE subcohort) were followed from the VTE date for additional outcomes including anticoagulation use, HCRU, and major bleeding (defined in the Supporting Information[37-39]). Anticoagulation was classified as outpatient LMWH, vitamin K antagonist (VKA) or DOAC at 30 days after VTE diagnosis, to capture long-term treatment patterns. HCRU included the following measures: primary care physician visits (n), emergency room visits (n), and hospitalizations (n, length of stay).

2.5 | Statistical analysis

Categorical variables were reported as frequency and percentage, and continuous variables as mean (standard deviation [SD]) or median (IQR). Descriptive analyses were conducted to compare the demographic, clinical, and treatment characteristics for the study cohort for those who experienced a VTE event in the 1-year period following the index date with those who did not. Baseline descriptive characteristics were compared using *t* tests for continuous variables and chi-square tests for discrete variables.

Cumulative incidence of VTE (95% confidence interval [CI]) at 12 months was calculated and stratified by Khorana score risk group, with death as a competing risk. Multivariable time-to-event analysis calculated hazard ratios (HRs) and 95% CIs for associations between baseline variables and VTE using competing risks analysis (using the Fine and Gray model), with death as a competing risk. All variables in Table 1 were considered.

Time on any anticoagulation treatment after the VTE date was assessed in the VTE subcohort using Kaplan-Meier methodology, and median time on treatment with 95% CI presented.

To examine HCRU, patients in the VTE subcohort were matched 1:1 to patients in the main cancer cohort who did not experience a VTE (non-VTE subcohort) in the 24 months after index, on birth year, sex, type of malignancy, and geographical district of residence. Descriptive analysis for HCRU outcomes were assessed for the

TABLE 1 Baseline characteristics

	VTE[a] (n = 15 388), n (%)		
	No (n = 15 050)	Yes (n = 338)	*P* value[b]
Sex			
Male	5162 (34.3)	173 (51.2)	<.001
Age, y			
Median (IQR)	60 (49-68)	63.5 (56-72)	<.001
>65	4901 (32.6)	147 (43.5)	<.001
District			
Center	10 004 (66.5)	202 (59.8)	.007
North	2846 (18.9)	67 (19.8)	
South	2200 (14.6)	69 (20.4)	
Socioeconomic status			
Low	4844 (32.2)	121 (35.8)	.09
Medium	5609 (37.3)	132 (39.1)	
High	4597 (30.5)	85 (25.1)	
Deyo-Charlson comorbidity index[c]			
Mean (SD)	3.62 (2.51)	4.66 (2.93)	<.001
≤2	7423 (49.3)	108 (32.0)	<.001
3-4	4226 (28.1)	102 (30.2)	
≥5	3401 (22.6)	128 (37.9)	
Comorbidities[d]			
Diabetes mellitus	2690 (17.9)	63 (18.6)	.77
Hypertension	6123 (40.7)	169 (50.0)	.001
Smoking			
Current or past smoker	5730 (38.1)	131 (38.8)	0.02
Never	9230 (61.3)	201 (59.5)	
Unknown	90 (0.6)	6 (1.8)	
BMI[e]			
Measured	13982 (92.9)	318 (94.1)	.47
Mean (SD)	27.36 (5.30)	28.62 (5.35)	<.001
Drug purchases[f]			
Estrogen	399 (2.7)	4 (1.2)	.13
Prior major bleed			
Any	389 (2.6)	11 (2.8)	.55
Hemorrhagic stroke	50 (0.33)	2 (0.52)	.97
GI bleeding	175 (1.16)	4 (1.03)	
GU bleeding	121 (0.80)	4 (1.03)	
Other bleeding	42 (0.28)	1 (0.26)	
Khorana score			
Low-risk (0–1)	12 010 (79.8)	183 (54.1)	<.001
Intermediate-high-risk (≥2)	3040 (20.2)	155 (45.9)	
Malignancy type			
Hematological	2220 (14.8)	40 (11.8)	.25
Solid	12741 (84.7)	297 (87.9)	
Breast	6704 (44.5)	40 (11.8)	
Digestive Organs[g]	1594 (10.6)	104 (30.8)	
Respiratory system	1139 (7.6)	53 (15.7)	
Brain and nervous system	374 (2.5)	23 (6.8)	
Missing	89 (0.6)	1 (0.3)	
Anticancer treatment			
Chemotherapy ± mAbs	6913 (45.9)	224 (66.3)	<.001
Hormonal treatment	4962 (33.0)	37 (10.9)	
mAbs	1228 (8.2)	25 (7.4)	
Targeted treatment	647 (4.3)	17 (5.0)	
Missing	1300 (8.6)	35 (10.4)	

Note: Baseline demographic and clinical characteristics of patients (n = 15 388) with a cancer diagnosis in 2010–2018, age ≥18 years by first VTE.[a]

Abbreviations: BMI, body mass index; GI, gastrointestinal; GU, genitourinary; IQR, interquartile range; mAbs, monoclonal antibodies; SD, standard deviation; VTE, venous thromboembolism.

[a]VTE within 12 months after initiating first-line anticancer treatment.

[b]Univariate analysis comparing baseline variables in patients with and without VTE at 12 months.

[c]Without malignancy or HIV.

[d]From MHS registries, ever before index date.

[e]Closest within 5 years before index date.

[f]Within 3 months before index date.

[g]Digestive cancer included intestine, pancreas, and stomach cancers.

1-year period following the VTE event and compared between the VTE subcohort and matched non-VTE subcohort. Follow-up time was matched between the subcohorts to account for patients in the VTE subcohort who died within the follow-up period. Characteristics were compared using *t* tests for continuous variables and chi-square tests for discrete variables.

All analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY, USA) or R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria), and a *P* value <.05 was considered statistically significant.

The study was approved by the local ethics review board of MHS in Israel.

3 | RESULTS

3.1 | Cohort characteristics

A total of 15 388 eligible patients were identified from the Israeli National Cancer Registry with a primary cancer diagnosis. Median age was 60 years, 65% were women, mean comorbidity index was 3.6, and 38% had an indication of current or former smoking. In this cohort, 20.8% had an intermediate-high Khorana score (≥2) and 46% received chemotherapy. A total of 338 patients (2.20%) had a VTE within 1 year after first-line anticancer treatment initiation. Deep vein thrombosis was the most common diagnosis in 256 (75.7%) patients followed by pulmonary embolism with/without deep vein thrombosis in 82 (24.3%; data not shown). Table 1 shows the baseline patient characteristics stratified for VTE within 1 year after index.

3.2 | VTE incidence and risk factors

The cumulative incidence of VTE at 12 months was 2.20% (95% CI, 1.96%-2.43%) for the full cohort (Figure 1), 4.88% (4.14%-5.63%) for patients with intermediate-high-risk Khorana score, and 1.49% (1.28%-1.71%) for low-risk Khorana score patients (Figure 2). When stratified by malignancy type, digestive, brain, and respiratory cancer had the highest cumulative incidence of VTE at 12 months after the index date (Figure S1). Univariate analysis of variables associated with VTE is shown in Table 1. Intermediate-high-risk Khorana score, first-line chemotherapy, certain malignancy types (ie, digestive organs, respiratory system, brain), age >65 years, increased comorbidity index, geographical district of residence (ie, south of Israel), and unknown smoking status were all associated with an increased risk of VTE on multivariable analysis, as detailed in Table 2.

A total of 2862 (19%) patients with no VTE and 34 (10%) with VTE at 12 months received primary outpatient thromboprophylaxis at some stage during the 12-month period before VTE. Most of these patients were treated with LMWH (85%) for a median (IQR) of 30 (30–92) days (data not shown). Patients who received thromboprophylaxis treatment were older, had a lower socioeconomic status, had a higher comorbidity index, had a higher Khorana score, and were more likely to receive chemotherapy treatment (see Table S1).

3.3 | Anticoagulation patterns in patients with VTE

In the VTE subcohort (n = 338), 36 (10.7%) patients died without initiating anticoagulation. The median time to initiating anticoagulation was 1 day (IQR, 0-5; data not shown). Among those who initiated anticoagulation (n = 302), the median time on any continuous anticoagulation was 17.6 months (95% CI, 14.0-26.6), while 243 (80.5%) continued treatment for at least 1 month. In Figure 3, which depicts the time on continuous anticoagulation since VTE diagnosis, it is evident that beyond ≈24 months, the proportion of patients receiving anticoagulation stabilizes at >25%, for those with a long enough follow-up. At 1 month after VTE, the majority of anticoagulated patients were receiving LMWH (n = 200; 82.3%), while 23 (9.5%) and 20 (8.2%) were treated with VKAs and DOACs, respectively (Table S2). The percentage of patients in the VTE subcohort receiving DOACs before and after January 1, 2016, was 2.7% and 27.3%, respectively (data not shown). In the VTE subcohort, 9 (3%) patients experienced major bleeding (data not shown).

3.4 | HCRU in patients with VTE

The baseline characteristics in the VTE and matched non-VTE subcohorts (n=301 each) are shown in Table S3. No match was found for 37 of 338 patients with VTE in the full cohort. All HCRU parameters were significantly higher at 12 months for patients in the VTE subcohort as compared to their matched controls, as detailed in Table 3. This included a higher mean (SD) number of primary care

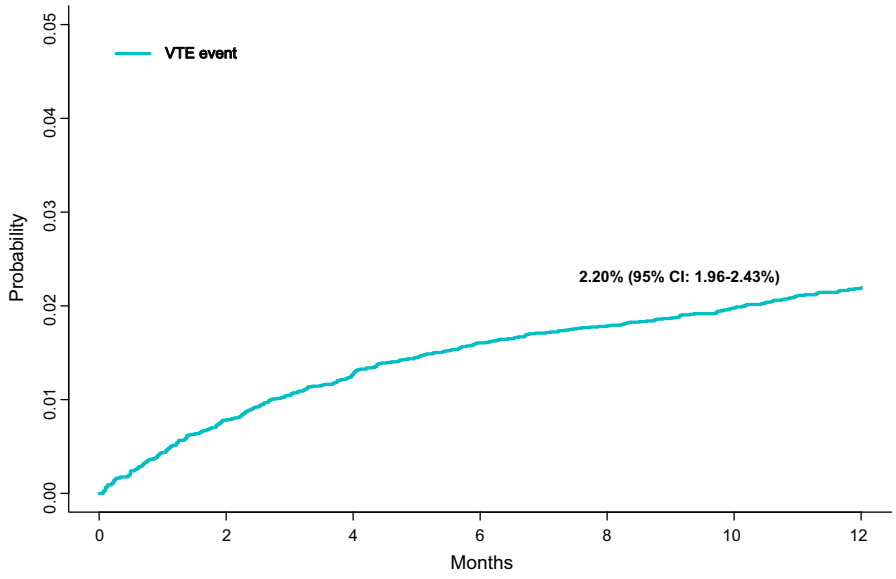

FIGURE 1 Cumulative incidence of VTE events for the whole VTE cohort, n = 15 388. Cumulative incidence of VTE events within the first year from cancer treatment initiation for patients with cancer in 2010 to 2018, age ≥18 y, with death as a competing risk, n = 15 388. KS, Khorana score; VTE, venous thromboembolism

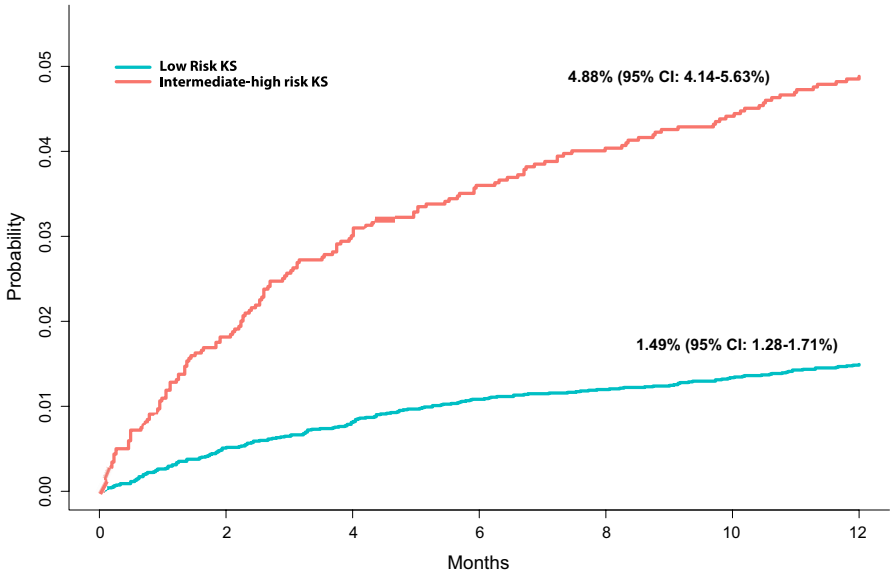

FIGURE 2 Cumulative incidence of VTE events stratified by Khorana score, n = 15,388. Cumulative incidence of VTE events within the first year from cancer treatment initiation for patients with cancer in 2010 to 2018, age ≥18 y, split by Khorana score, with death as a competing risk, n = 15 388. KS, Khorana score; VTE, venous thromboembolism

physician visits (21.9 [17.56] vs 13.27 [12.47]), more patients with at least one emergency room visit (125 [41.5%] vs 58 [19.3%]), more patients with at least one hospitalization (245 [81.4%] vs 106 [35.2%]), and longer mean (SD) length of hospital stay (20.14 [26.48] days vs 13.08 [17.77] days).

4 | DISCUSSION

This population-based historical cohort study of patients with newly diagnosed cancer initiating first-line anticancer treatment demonstrated a 12-month VTE cumulative incidence of 2.2%. Variables associated with VTE were increasing age, higher Charlson comorbidity index, intermediate-high Khorana score, receiving chemotherapy, certain malignancy types, unknown smoking status, and residence in the south of Israel. Median time on anticoagulation after VTE was >1 year, while HCRU was significantly higher in the VTE subcohort as compared to their matched cancer controls without VTE.

4.1 | VTE incidence and risk factors

The 12-month VTE incidence in the current study was comparable to prior studies, such as a 2.3% (95% CI, 2.2%-2.3%) 12-month VTE incidence in a recent Danish cohort study of patients with newly diagnosed cancer.[12,40,41] The relatively low VTE incidence compared to some other studies[42-44] may be due to the fact that 49% of our cohort included patients with early-stage breast and prostate cancer who received adjuvant hormone therapy. Nonetheless, some adjuvant hormonal therapies, exemplified by tamoxifen, carry an increased risk of VTE, while others (such as aromatase inhibitors) are not clearly associated with VTE.[45] Previous reports have similarly identified an association between chemotherapy and VTE in cancer.[1,14,41] The Khorana score has also been shown to predict VTE in multiple prior studies, albeit with suboptimal performance.[46] Incidence of VTE by cancer site has been widely reported, and we confirm similar findings.[11,12] Increasing age and Charlson comorbidity index were risk factors for VTE in some studies[1,41] as in ours. There was no difference between sex, similar to some previous studies.[1,41] The association between residence in the south of the country and VTE is relevant only to the Israeli setting. This finding may reflect health care disparities, since this region has less access to tertiary health care. This region also has a higher proportion of patients with a low socioeconomic status in our study, which was associated with a higher VTE incidence in a previous study.[47] In our study, the socioeconomic status was numerically but not statistically lower in patients with VTE, but this was measured according to area of residence and does not capture patient-level factors. Unknown smoking status, as compared to past or current smokers, was an unexpected VTE risk factor, which may represent residual confounding, such as less access to health care resulting in no documentation of smoking status. Prior VTE is a risk factor identified in the Danish cohort that was not addressed in our study, since we excluded patients with prior VTE. This was done to eliminate possible bias in management of patients at highest risk of VTE (eg, thromboprophylaxis or increased awareness) and misclassification of recurrent VTE events in patients with prior VTE codes.

Taken together, the current study demonstrates that multiple clinical factors are associated with VTE incidence in patients with cancer, even after accounting for the Khorana score. These factors should be considered in the development of future VTE risk assessment models considering clinical variables, patient genetics (eg, inherited thrombophilia),[48] and tumor-specific factors (eg, somatic mutational profile).[49]

The use of outpatient thromboprophylaxis is an important confounder to consider when interpreting the study results. We found that the majority of patients did not receive thromboprophylaxis, in line with current guidelines over the study period that recommended VTE prophylaxis for hospitalized patients with cancer but not for most outpatients.[42,50] In our study, a numerically higher percentage

TABLE 2 Variables associated with VTE[a] on multivariable analysis

Variable	HR (95% CI)
Female sex (ref. = male)	0.99 (0.78-1.26)
Age >65 y (ref. = ≤65 y)	1.26 (1.00-1.59)
District (ref. = center)	
North	1.11 (0.83-1.47)
South	1.39 (1.05-1.85)
Socioeconomic status (ref. = low)	
Medium	1.09 (0.85-1.41)
High	1.01 (0.75-1.36)
Deyo-Charlson comorbidity index[b]	1.04 (1.01-1.08)
Smoking before index (ref. = ever)	
Never	1.19 (0.94-1.51)
Unknown	2.78 (1.28-6.04)
Intermediate-high-risk Khorana score (ref. = low risk)[c]	1.66 (1.30-2.13)
First-line anticancer treatment (ref. = chemotherapy ± mAb)	
Hormone treatment	0.64 (0.43-0.93)
mAbs	0.69 (0.45-1.08)
Targeted treatment	0.64 (0.39–1.07)
Unknown	0.79 (0.55-1.15)
Malignancy type (ref. = breast)	
Digestive organs	6.02 (3.84-9.46)
Respiratory system	4.84 (2.89-8.11)
Brain	5.01 (2.73–9.18)
Other	2.89 (1.87–4.47)

Note: Multivariable model with hazard ratios for predictors of VTE[a] using competing risks analysis (n = 15 388).

Abbreviations: CI, confidence interval; HR, hazard ratio; mAbs, monoclonal antibodies; VTE, venous thromboembolism.

[a]VTE within 12 months after initiating first-line anticancer treatment.

[b]Without malignancy or HIV.

[c]Intermediate-high risk was defined as Khorana score ≥2.

of patients without VTE received primary outpatient thromboprophylaxis (mainly LMWH) at 12 months, compared to patients with VTE (19% vs 10%). On the one hand, thromboprophylaxis in itself reduces VTE incidence by ≈50%.[51] On the other hand, this may be a marker of patients at a higher perceived risk of VTE or even of those with a clear-cut indication, such as postoperative thromboprophylaxis. The latter is supported by the characteristics of patients receiving thromboprophylaxis in our study, as median length of prophylaxis was 30 days (IQR, 30-92), which is in line with the 30 days of thromboprophylaxis recommended after abdominopelvic surgery.[22]

4.2 | Anticoagulation patterns in VTE patients

In our VTE patient population, 10.7% died without initiating anticoagulation treatment. This is a lower proportion compared to a third of patients as reported previously.[52] This discrepancy can be partially explained by a younger mean age of our study population (60 vs 70 years) and differences in study design. We found that time to outpatient treatment from VTE diagnosis was 1 day, showing quick initiation of outpatient treatment by the physician. Median time on treatment for patients with a VTE was 17.6 months, much longer than a previously published study of treatment patterns,[52] although this previous study had a much shorter follow-up (up to 7.1 months). Most current clinical guidelines recommend the use of LMWH or DOACs for at least 3 to 6 months after CAT,[22,25,26] with continued treatment dependent on active malignancy, cancer site, bleeding risk, tolerability, anticancer treatment, persistent risk factors for recurrence, and patient preference.[26,53-55] An overview of available studies that focused on treatment length concluded that this question remains open and physicians should weigh the risk-benefit ratio, taking into account all of the above factors.[56] In addition, the drug-drug interactions with anticancer treatment should be taken into account, particularly as length of time from the initial CAT increases, risk of VTE recurrence decreases, especially after 6 months.[57] The authors of another study proposed an algorithm (adapted from a previous study) for treatment choice whereby if the risk of bleeding is low, cancer location is considered low risk for bleeding, and there are no expected drug-drug interactions, DOACs are recommended, and if the answers to any of these factors are positive, LMWH should be considered.[58] A study in Canada reported that extended therapy is indicated for most patients with CAT and most patients received LMWH, but nonadherence was not rigorously monitored.[59]

In our study, 82% of patients with VTE received LMWH, 10% VKAs, and 8% DOACs, in line with LMWH being the standard of care for treatment of cancer-associated VTE during the study period (2010-2018), before the landmark studies on DOACs for CAT were published, leading to changes in guidelines.[60-62] This rate of DOAC use is a bit lower than that seen in some recent cohort studies carried out during the time of our study.[63,64] Possible reasons for this difference are as follows: Our study period (ie, indexing) commenced in 2010 and ended in December 2018, meaning that 12-month VTEs could occur until December 2019. DOAC treatment for VTE in the general non–cancer-specific population was approved in Israel from 2009, and reimbursed from 2018; however, cancer-specific evidence has been available only since mid-December 2017 when the Hokusai-Cancer study was published.[61] Use in Israel has gradually increased since then, and this is reflected by the increase in proportion of DOAC-treated patients with CAT in our cohort, from 2.7% before 2016 and reaching 27.3% from 2016 until the end of the study period. The utilization of DOACs in CAT is anticipated to rise, in light of these studies and updated international guidelines.[22-24]

4.3 | HCRU in patients with VTE

There are limited prior data suggesting that patients with cancer and VTE have higher HCRU than those without VTE. One study reported significantly higher health care costs (including pharmacy, inpatient,

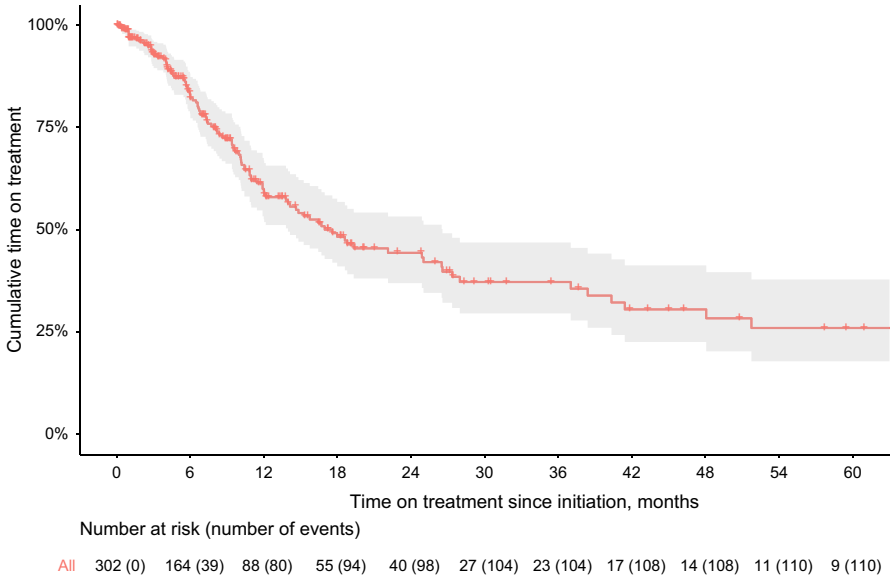

FIGURE 3 Time on anticoagulation treatment for the VTE cohort. Time on any continuous anticoagulation treatment for the VTE cohort, 2010 to 2018, age ≥18 years, n = 302; 93.10% (95% CI, 96.20%-90.00%) were still on treatment at 3 months, 83.10% (88.20%-78.40%) at 6 months, and 59.30% (66.90%-52.60%) at 12 months

TABLE 3 Health care utilization for VTE matched cohort

Variable	Non-VTE subcohort (matched controls; n = 301)	VTE subcohort (cases; n = 301)	*P* value
Primary care physician visits in the community			
≥1, n (%)	274 (91.0)	277 (92.0)	.66
Number of visits, mean (SD)[a]	13.27 (12.47)	21.9 (17.56)	<.001
≥10 visits, n (%)	158 (52.5)	213 (70.8)	<.001
Emergency room visits			
≥1, n (%)	58 (19.3)	125 (41.5)	<.001
Number of visits, mean (SD)[a]	0.3 (0.77)	0.71 (1.11)	<.001
Hospitalization			
≥1, n (%)	106 (35.2)	245 (81.4)	<.001
Number of separate admissions in the follow-up year, mean (SD)	1.7 (1.1)	2.6 (2.2)	<.001
Length of stay, d, mean (SD)[a]	13.1 (17.8)	20.1 (26.5)	.01

Note: Health care utilization for the VTE matched cohort for the 12-month follow-up period after VTE event, n = 602.
Abbreviations: SD, standard deviation; VTE, venous thromboembolism.
[a]For those who used particular health care.

emergency department, and outpatient costs) in patients with cancer who developed a VTE within 3.5 months from the index date (first day of chemotherapy treatment)[27] compared to those who did not. Another study reported additional cost of hospital stays for patients with cancer and a VTE, suggesting economic justification for the use of preventative treatment for CAT.[28] Other studies reported an increased number of emergency room visits and admissions for patients with cancer and a VTE[29] and increased all costs for patients with lung cancer and a VTE.[30]

In the current study, potential confounders such as anticancer treatment and comorbidity index were balanced between the two cohorts. Khorana score was higher in the VTE cohort, even though the cohorts were matched for malignancy type. Health care utilization was significantly higher in the VTE subcohort than in the non-VTE subcohort, with our results indicating a significantly higher number of emergency room visits and hospitalizations for patients with a VTE as compared to those without. In addition, the fact that >25% of the VTE cohort (for those with a long enough follow-up) were still receiving anticoagulation at 2 to 6 years after VTE represents a health care burden with respect to anticoagulation costs and possible anticoagulation-associated bleeding complications. This study adds to previous findings in different settings and generates the hypothesis that prevention of cancer-associated VTE may reduce HCRU.

Furthermore, there is increased VTE recurrence, HCRU, and costs for nonadherent patients in all patients with VTE,[65] and particularly for patients with cancer who have increased complications.

VTE has traditionally been treated in patients with cancer with LMWH; however, recent studies show that rivaroxaban is associated with lower hospitalizations, length of stay, emergency room visits, and outpatient visits as compared to both LMWH and warfarin[66,67] and may also have the added value of increased adherence[68] and persistence.[69]

4.4 | Strengths and limitations

Strengths of this study include the large sample size of 15 388 patients with cancer followed longitudinally in a comprehensive database. MHS comprises 25% of the patient population in Israel and shows real-world generalizability within the population.[31] Limitations of the current analysis include the retrospective nature of the study, including reliance on administrative coding particularly for VTE diagnosis. However, the VTE algorithm used has been previously validated and is considered accurate, although it was not validated in our database.[35] Furthermore, patients with VTE with active bleeding or a high risk of bleeding may not be treated with anticoagulation, and thus are not captured in our study since this algorithm mandates anticoagulation or death with 30 days of VTE. We could not determine cancer stage. Data on purchases made outside of MHS pharmacies were not captured; however, patients are unlikely to buy medications outside of MHS due to their discounted price within MHS. It should also be noted that actual medication use is unknown, as dispensed medications may not be consumed; however, previous studies have demonstrated the validity of this approach for measuring compliance with chronic medications.[70] Finally, the Khorana score was developed to assess risk over 3 months from initiation of anticancer therapy and has been used to assess risk for up to 6 months.[17,18] We used the Khorana score to predict VTE up to 12 months from treatment initiation, which may have underestimated the risk as the platelet, hemoglobin, and leukocyte counts and BMI may change over this time.

5 | CONCLUSION

The 12-month cumulative incidence of VTE was 2.2%. Older age, comorbidity index, intermediate-high-risk Khorana score, certain malignancy types, and chemotherapy were significantly associated with the risk of a VTE event in the year after initiation of anticancer treatment. The Khorana score prediction model was appropriate for use in this cohort. VTE was associated with long-term use of anticoagulation, and health care utilization was significantly higher for patients in the VTE subcohort as compared to their matched controls.

RELATIONSHIP DISCLOSURE

AL is an employee of Rabin Medical Center who was paid as a consultant to Pfizer in connection with this study and declares personal fees for scientific advisory boards from Bayer and Sanofi, outside the scope of this work. PR received a research grant from Pfizer and has participated in advisory boards outside the scope of this work. GS has participated in advisory boards outside the scope of this work. OFM and MT are employees of Pfizer Israel. The remaining authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization and design: SSM, GC, OFM, MT, AL; analysis and interpretation: SSM, GC, OFM, MT, AL, GS, PR; writing and revising the content: SSM, GC, OFM, MT, AL, GS, PR; final approval: SSM, GC, OFM, MT, AL, PR, GS. All authors have read and agreed to the published version of the manuscript.

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SUPPORTING INFORMATION

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