Trends and updates on the epidemiology of cancer-associated thrombosis: a systematic review

Ang Li,[1] Emily Zhou[2]

[1]Section of Hematology-Oncology, Department of Medicine, Baylor College of Medicine, Houston, TX; [2]McGovern Medical School, University of Texas Health Science Center, Houston, TX, United States

ABSTRACT

For cancer patients, cancer-associated thrombosis (CAT) is a serious complication. An updated epidemiology of CAT over the last ten years is summarized in this review. A comprehensive analysis of pertinent population cohort research released between 2011 and 2024 was carried out. In patients with unselected cancers, the 12-month incidence of CAT is roughly 3-5% (9-fold increase vs to the matched non-cancer population); however, in patients with advanced cancers requiring systemic therapy, the risk rises to 6-8% (20-fold increase *vs*. to the matched non-cancer population). Anticoagulation use and adherence have improved, but the risk of recurrence is still high, at 5-8% at 6 months and 7-15% at 12 months. The type, stage, and treatment of cancer, a history of venous thromboembolism (VTE), prolonged hospitalization or immobilization, and obesity are significant clinical predictors of the development of CAT. The modified Vienna-CATS and EHR-CAT have the best performance (area under the curve 0.68-0.71) among the clinical risk prediction scores for CAT using the original Khorana score backbone that has been externally validated. However, additional research is required to guarantee appropriate implementation and utilization of these models. Even with contemporary antineoplastic treatments, CAT is still a major complication for cancer patients. We encourage interdisciplinary partnerships among hematologists, data scientists, epidemiologists, and oncologists to guarantee the integration of customized VTE risk evaluation into standard oncologic treatment.

Correspondence: Ang Li, Baylor College of Medicine, One Baylor Plaza, 011DF, Houston, TX 77030, United States.
Tel.: +1.713.7983667.
E-mail: ang.li2@bcm.edu

Conference presentation: paper presented at the 12th International Conference on Thrombosis and Hemostasis Issues in Cancer (17-19 May 2024, Bergamo, Italy).

Key words: epidemiology; incidence; neoplasms; thrombosis; thromboembolism.

Acknowledgments: this research was, in part, funded by NIH NHLBI K23 HL159271 and NIH Agreement No. 3OT2OD032581-01S1. AL, a CPRIT Scholar in Cancer Research, was supported by the Cancer Prevention and Research Institute of Texas (RR190104). The views and conclusions contained in this document are those of the authors and should not be interpreted as representing the official policies, either expressed or implied, of the NIH or CPRIT.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

Received: 31 January 2024.
Accepted: 29 February 2024.

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Licensee PAGEPress, Italy
Bleeding, Thrombosis and Vascular Biology 2024; 3(s1):108
doi:10.4081/btvb.2024.108

Introduction

Cancer-associated thrombosis (CAT) is defined as venous thromboembolism (VTE) involving pulmonary arteries (PE), deep veins of the legs (LE-DVT) or arms (UE-DVT), and sometimes abdominal or splanchnic veins (SpVT) during initial cancer diagnosis or active cancer treatment. In one estimate, CAT accounts for as many as 20% of all VTEs that affect 900,000 people from the United States each year.[1] Since VTE mostly occurs within the first year of cancer diagnosis, its development may lead to prolonged hospitalization, delayed treatment initiation, and consequently a detrimental effect on the quality of life and survival of cancer patients.[2,3] Given significant changes in anti-neoplastic treatment over the past decade, an increased understanding of the updated epidemiology of CAT in the modern era through this systematic review is crucial for both hematologists and oncologists.

The current review will describe the updated incidence, trends, risk factors, recurrence, and mortality of CAT in patients with active cancers. Treatment of CAT is beyond the scope of this review. We will primarily focus on population observational cohort studies with large sample size and valid methodological study designs. We will present both absolute and relative risks when available.

Methodology

A systematic review was performed using Title and MeSH term search with ("neoplasm" OR "cancer") AND ("thrombosis" OR "thromboembolism") AND ("epidemiology" OR "cohort studies" OR "incidence" OR "recurrence" OR "mortality" OR

"risk factors") in MEDLINE/PubMed for published studies in the English language from 2011 to 2024. Retrospective cohort studies >10,000 patients or prospective cohort studies >1,000 were preferentially included. The inclusion criteria for study size were set lower for prospective studies because they require greater effort and expenses and thus often have smaller study populations than retrospective studies. Abstracts only, review articles, clinical trials, case-control studies, systematic reviews, and studies isolated to singular cancer types were excluded. Cited references were further examined for additional inclusion. When multiple studies referenced the same cohort or population database, the most updated one was chosen. Two reviewers (AL and EZ) screened the title and abstract of the 380 resulting articles (date of search 1/15/24) and chose the relevant studies in this review.

Definition of cancer-associated thrombosis in studies

A total of 11 studies (7 retrospective and 4 prospective) were included to assess the incidence of CAT (Table 1). These studies represented diverse geographic locations across the world, including the United States (USA), the United Kingdom (UK), Denmark, Austria, Italy, France, Israel, Japan, and Taiwan. The definition of

Table 1. Incidence and trend of cancer-associated thrombosis in selective population studies.

Author	Location	Design	N	Year	Study population	VTE definition[1]	VTE trend	Incidence at 12 mo[2]
All cancers at time of diagnosis								
Martens JAMA Open 2023	USA	Retrospective cohort	434,203	2006-2021	US veterans with newly diagnosed solid + heme cancers Median age 67; 97% male; 26% metastatic	Inpatient or outpatient PE, LE-DVT, and UE-DVT (excluding abdominal thrombosis) (ICD code + NLP algorithm)	Minor increase 4.2% to 4.7%	4.5% VTE3.6% PE/LE-DVT
Mahajan Blood Adv 2022	California, US	Retrospective cohort	942,109	2005-2017	California residents with newly diagnosed solid + heme cancers Median age 65; 47% male; 20% metastatic	Inpatient + emergency department PE, LE-DVT (ICD code)	Major increase for most cancers	Cancer-specific PE/LE-DVT See Table 2
da Costa AJH 2021	Harris County, TX	Retrospective cohort	15,342	2011-2020	Harris county residents with newly diagnosed solid + heme cancers Mean age 54; 45% male; 29% metastatic; 74% uninsured; 84% disadvantaged neighborhood	Inpatient + outpatient PE, LE-DVT, UE-DVT, or non-tumor abdominal vein thrombosis (ICD code + chart review)	No change	11.2% VTE 8.1% PE/LE-DVT
Mulder Blood 2021	Denmark	Retrospective cohort	499,092	1997-2017	Danish residents with newly diagnosed solid + heme cancers Median age 68; 49% male; 21% metastatic Comparison cohort matched on age, sex, year	Inpatient or outpatient PE, DVT, abdominal thrombosis, and other VTE (ICD code)	Major increase 1.0% to 3.4%	2.3% VTE 2.8/100-py HR 8.5 *vs.* matched non-cancer
Moser RPTH 2021	Israel	Retrospective cohort	15,388	2010-2018	Israel residents with newly diagnosed solid + heme cancers Median age 60; 35% male; 49% early stage on adjuvant hormone therapy	Inpatient + outpatient PE, LE-DVT, UE-DVT (ICD code)	N/A	2.2% VTE
Yu T&H 2012	Taiwan	Retrospective cohort	497,180	1997-2005	Taiwan residents with newly diagnosed solid + heme cancers (catastrophic illness database) Mean age 61; 56% male; unknown stage	Inpatient PE, DVT, abdominal thrombosis (ICD code)	Minor increase 0.3% to 0.6%	0.5%

To be continued on next page

CAT varied across the studies due to limitations in outcome ascertainment strategies. Most studies included inpatient and outpatient diagnosis of PE and LE-DVT, though some only reported hospital discharge diagnosis (missing outpatient diagnosis).[4-6] There was significant heterogeneity in the inclusion of UE-DVT and SpVT across the studies. Since 10-20% of patients with hepatobiliary and pancreatic cancers develop SpVT,[7] indiscriminate inclusion of SpVT in CAT outcome definition could lead to overinflated incidence estimation. Most of the retrospective cohort studies relied on country-specific International Classification of Diseases (ICD) codes to determine VTE outcomes, though a few also incorporated chart review or natural language processing verifications.[5,8,9] Most

Table 1. Continued from previous page.

Author	Location	Design	N	Year	Study population	VTE definition[1]	VTE trend	Incidence at 12 mo[2]
Ohashi Thromb Res 2022	Japan	Prospective cohort	9,630	2017-2019	Japanese residents with newly diagnosed solid cancers Mean age 67; 51% male; 23% metastatic	Inpatient or outpatient symptomatic PE, LE-DVT (adjudicated)	N/A	0.5%
Advanced cancers receiving systemic therapy								
Martens JAMA Open 2023 Subset	USA	Retrospective cohort	118,731	2006-2021	US veterans with newly diagnosed solid + heme cancers receiving systemic therapy within 3 months	See above	See above	7.7% VTE
Mulder Blood 2021 Subset	Denmark	Retrospective cohort	64,397	2011-2017	Danish residents with newly diagnosed solid + heme cancers receiving systemic therapy within 4 months	See above	See above	5.3% VTE 6.3/100-py HR 19.7
Cohen T&H 2017	UK	Retrospective cohort	112,738 person years	2001-2011	UK residents with "active" solid + heme cancer episodes (primary Dx of cancer as hospital discharge diagnosis; OR receipt of chemotherapy, radiation, or transplantation) Mean age 69; 49% male; unknown stage	Inpatient PE, LE-DVT, UE-DVT (excluding cerebral and abdominal vein thrombosis) (ICD code + chart review)	N/A	5.8/100-py
Englisch Blood Adv 2022	Austria CATS	Prospective cohort	1,708	2003-2019	Vienna resident with newly diagnosed or recently progressed solid + heme cancers with 68% receiving chemotherapy during observation Mean age 61; 46% female; 32% metastatic	Inpatient or outpatient PE, LE-DVT, UE-DVT (adjudicated)	N/A	7.8%
Verzeroli JTH 2023	Italy HYPERCAN	Prospective cohort	1,286	2012-2019	Italian residents with lung, colon, gastric, breast solid cancers receiving chemotherapy Median age 65; 55% male; 100% metastatic	Inpatient or outpatient PE, LE-DVT, symptomatic UE-DVT (adjudicated)	N/A	9.7% (6 months)
Van Es Haematologica 2017	Multinational	Prospective cohort	876	2008-2016	Netherlands, Italy, France, Mexico residents with solid cancers receiving chemotherapy last 3 months Mean age 64; 59% male; 66% metastatic	Inpatient or outpatient PE, LE-DVT, symptomatic UE-DVT (chart review or telephone contact)	N/A	6.5% (6 months)

[1]Most large epidemiology studies relied on the use of country-specific ICD codes from either inpatient or inpatient/outpatient data sources. Significant heterogeneity existed on the inclusion or exclusion of upper extremity DVT and abdominal venous thrombosis; [2]either cumulative incidence (%) or incidence rate (per 100-person-year) was provided depending on the individual study design. VTE, venous thromboembolism; mo, months PE, pulmonary embolism; DVT, deep vein thrombosis; LE-DVT, lower extremity deep vein thrombosis; UE-DVT, upper extremity deep vein thrombosis; ICD, international classification of diseases; NLP, natural language processing; US, United States; py, patient-year; HR, hazard ratio; OR, odds ratio.

of the prospective cohort studies required independent outcome adjudications. To ensure uniformity in outcome reporting, a 12-month follow-up window was chosen for this review to report the cumulative incidence (%) or incidence rate per 100-patient-year (py). Across all 11 studies, the cumulative incidence of CAT ranged from 0.5% to 11.2%. Given the differences in study populations across each study in the following sections, we will examine the data in further granularity by examining incidence rates in different cancer types, stages, and treatments.

Trend of cancer-associated thrombosis in active cancer

A few studies examined the trends of CAT over time. Mulder *et al*. reported a significant increase in 12-month CAT from 1.0% in 1997 to 1.9% in 2004 to 3.4% in 2017.[10] Mahajan *et al*. also reported an increase in CAT incidence from 2005-2017, although the rate of increase was cancer-dependent.[11] In contrast, Martens *et al*. reported a minor increase in CAT incidence from 4.2% in 2005 to 4.5% in 2017.[9] Advances in VTE awareness, imaging modalities, and anti-neoplastic treatment likely all contributed to the increase in CAT incidence over the past 2 decades. Nonetheless, changes in ICD codes used in studies could also have influenced the outcome reporting. For example, ICD-CM (USA) for VTE diagnosis had a significant expansion in years 2004, 2009, and 2015; therefore, it is important for studies to use epoch-specific ICD code for outcome ascertainment.

Incidence of cancer-associated thrombosis by cancer stage/treatment

Due to significant heterogeneity in the study populations, we divided the CAT incidence assessment into those with cohort entry at the time of diagnosis (all cancers) *vs*. at the time of systemic therapy (advanced cancers). Accounting for differences in study design, CAT occurrence appeared to have geographic variations. Among representative studies at the time of initial cancer diagnosis, the 12-month cumulative incidence of CAT was 4.5% in 1 study (USA),[9] 2.3% in 2 studies (Denmark, Israel),[10,12] and 0.5% in 2 studies (Taiwan, Japan).[6,13] One additional cohort study from Harris County, USA reported a higher incidence of 8.1% PE/LE-DVT at 12 months,[8] though the patient population was diverse (50% Hispanic, 28% Black), young (mean age 54), uninsured (74%) and living in disadvantaged neighborhoods (84%), and with more aggressive cancer and advanced stage (48%). In contrast to the studies reporting CAT incidence in all patients from time of cancer diagnosis, among representative studies at the time of systemic therapy treatment, the 12-month cumulative incidence of CAT was significantly higher ranging 5.8-7.8% in 4 studies (USA, Denmark, UK, Austria).[5,9,10,14] In two additional cohorts that included selective solid tumor patients with high proportion of metastatic disease, the 6-month cumulative incidence of CAT was even higher at 6.5% (MICA, 66% metastatic) and 9.7% (HYPERCAN, 100% metastatic).[15,16]

Taken together, relative to matched non-cancer populations, the hazard ratio (HR) for VTE was 8.5 for patients with cancers and 19.7 for patients with advanced cancers receiving systemic therapy.[10] Therefore, cancer patients with advanced disease requiring systemic therapy have a significantly higher risk of CAT than those with limited resectable disease. For example, gynecologic and non-prostate genitourinary cancers are considered "high-risk" in risk prediction models but "low-risk" in population studies (most of these cancers normally present at early stages).[9,17]

Incidence of cancer-associated thrombosis by cancer type

Cancer type is likely the most important determinant of CAT risk. Table 2 summarizes the 12-month cumulative incidence of CAT across different cancer types in 5 large epidemiology studies. Yu *et al*. did not report significant variations among cancer types in Taiwan.[6] Among solid tumors in the 4 other studies, pancreatic, stomach, biliary, and brain cancers consistently had the highest 12-month incidence of CAT (8-10%). Lung, colorectal, ovarian, sarcoma, lymphoma, and myeloma had the next highest incidence (5-7%). Non-prostate genitourinary cancers had variable risks depending on staging and treatment as discussed previously. Among leukemias, acute lymphocytic leukemia had the highest incidence of 12-month CAT at 18.6% (11.8% PE/LE-DVT) followed by acute myeloid leukemia at 7.3% (3.6% PE/LE-DVT).[9] It is important to note that UE-DVT (mostly catheter-associated thrombosis) was significantly more common in acute leukemias than most other cancer types due to prolonged insertion of indwelling peripherally inserted central catheter for chemotherapy administration. Overall, the previously identified very high risk and high-risk cancer types associated with CAT continue to be associated with greater incidences of CAT in Western countries.

Risk factors of cancer-associated thrombosis occurrence

As discussed above, different cancer types, stages, and treatments are all important drivers for CAT development and contribute to the varying incidences of CAT. The relative impact of each can only be discerned in studies adequately powered to adjust for each factor. Table 3 highlights studies that examined the cancer- and patient-specific risk factors for CAT. In cohort studies, the specific cancer type had the highest association. For example, pancreatic cancer and stomach cancer had a 6-9-fold and 4-5-fold increase in CAT risk *vs*. prostate cancer, respectively. Cancer stage was the second most significant cancer-specific predictor with a 2-fold increase for stage III and a 4-fold increase for stage IV (*vs*. stage I). A case-control study by Ashrani *et al*. (not included in Table 3) reached a similar finding as these cohort studies.[18] In contrast, treatment type (received within the first 3-4 months of diagnosis) had a more attenuated effect. Cytotoxic chemotherapy, immune checkpoint inhibitor, and targeted/endocrine therapy had 1.5-2-fold, 1.5-fold, and 1.2-fold increased risks, respectively, compared to no treatment. Two recently published comparative cohort studies further demonstrated that patients receiving immunotherapy had a similar or slightly lower risk of VTE as those receiving cytotoxic chemotherapy in the first-line setting.[19,20] Based on these studies, we can conclude that while treatment choice impacts CAT risk, the underlying disease (cancer histology) and aggressiveness (cancer stage) likely had significantly higher association.

In addition to cancer-specific risk factors, there are also more

traditional patient-specific risk factors for VTE. Unsurprisingly, the strongest risk factor was the history of VTE at 2-8-fold increased risk.[8-10] Other risk factors included older age, male sex, higher body mass index, and recent hospitalization (each ~1.2-fold higher risk). Interestingly, comorbidity score (marker of underlying comorbid illness) and area of deprivation index (social determinant of health) had no association with CAT.[8,9]

Racial disparity and cancer-associated thrombosis incidence

The impact of race and ethnicity on the development of CAT (or VTE in general) remains a debated topic. Previous papers have posited that biological and sociological mechanisms contribute to racial disparities in incidence rates of CAT events. It is important to remember that race is inherently a sociopolitical construct and that racial and ethnic categories do not always correlate with genetic differences. While the reports of lower CAT risk among east Asians were consistent in studies across USA, Europe, and Asia (Table 1 and Table 4), the comparison between non-Hispanic Black (NHB) and Hispanic *vs*. non-Hispanic White (NHW) has mostly been reported in epidemiology studies in the USA. Specifically, the adjusted HR for CAT for Asians *vs*. NHW was 0.6-0.8 across multiple studies.[4,8,9,21] In contrast, the adjusted HR for NHB *vs*. NHW was consistently elevated at 1.2-1.4. Finally, the comparison between Hispanic *vs*. NHW was less pronounced with adjusted HR of 0.9-1.0. In absolute terms, Raskob *et al*. also reported highest incidence of CAT in NHB (40.9/100,000-py), followed by NHW (32.5/100,000-py), Asian Pacific islanders (7.7/100,000-py), and Hispanics (5.6/100,000-py) among active cancers in a population surveillance study in Oklahoma.[22]

Table 2. Incidence of cancer-associated thrombosis in individual cancers at 12 months in selective studies.

	Martens	Mahajan	Mulder	Cohen	Yu
	PE, LE-DVT, UE-DVT	PE, LE-DVT	PE, LE-DVT, UE-DVT, SpVT	PE, LE-DVT, UE-DVT	PE, LE-DVT, UE-DVT, SpVT
Location	US	US	Denmark	UK	Taiwan
Number	434,203	942,109	942,109	112,738 py	497,180
Breast	3.4	1.0	1.0	3.2	0.7
Lung	6.9	6.8	2.2-3.3	10.1	1.5
Prostate	1.5	1.0	1.2	4.4	1.4
Testicular	5.3		1.3		1.0
Bladder	5.8	5.1	2.7	2.7	0.9
Kidney	3.9	3.6	2.7		1.2
Colorectal	6.7	3.9	2.8	6.7	1.0
Esophageal	10.0		3.0		0.6
Stomach		6.7	3.2	10.8	1.1
Pancreas	12.1	10.7	5.5	14.6	1.2
Bile/gallbladder	9.1		3.8		
Liver	2.7		3.4		1.0
Neuroendocrine	4.3				
Ovarian		8.2	3.9	11.9	1.8
Uterine	4.9	3.7	2.0	7.0	
Cervical			2.0		1.8
Head & Neck	4.1				0.4
Sarcoma	6.2				1.4
Melanoma	1.7		0.6		0.8
Brain	11.1	9.7	3.3	12.1	1.3
Endocrine	1.6				0.3
Myeloma	7.7	5.3	3.8		1.6
NHL	11.0	4.3	3.2		1.0
HL	9.5		3.8		
ALL	18.6			4.5	
CLL	2.0				
AML	7.3				
MDS	2.7		1.7		0.9
CML	2.1				

PE, pulmonary embolism; LE-DVT, lower extremity deep vein thrombosis; UE-DVT, upper extremity deep vein thrombosis; SpVT, splanchnic veins; US, United tates; UK, United Kingdom; py, patient-year; NHL, non-Hodgkin lymphomas; HL, Hodgkin's lymphoma; ALL, acute lymphoblastic leukaemia; CLL, chronic lymphocytic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; CML, chronic myelogenous leukemia.

Validated clinical risk prediction scores for cancer-associated thrombosis

The American Society of Hematology 2021 Guidelines suggest thromboprophylaxis (conditional recommendation, moderate certainty of evidence) with a low-dose direct oral anticoagulant (DOAC) if the 6-month VTE risk is high (defined as 9.5% or higher by the consensus panel) while the bleeding risk is low-to-moderate.[23] Since the original Khorana score in 2008,[17] there have been various adaptations and improvements, including the Vienna CATS in 2010,[24] PROTECHT in 2012,[25] COMPASS-CAT in 2017,[26] modified Vienna CAT in 2018,[27] ONCOTHROMB in 2023,[28] and electronic health record (EHR) CAT in 2023.[29] Each of these risk scores relied primarily on the cancer type (with variation based on the inclusion criteria of each study) as the backbone of the models. Three risk scores included additional biomarkers such as P-selection,[24] D-dimer,[27] and a 9-single nucleotide poly-

Table 3. Risk factors for cancer-associated thrombosis in selective studies (multivariable regression).

Location	Martens US	da Costa US	Mulder Denmark
Number	434,203	15,342	942,109
Cancer type/site			
Breast	1.85 (1.62-2.10)	Baseline	1.56 (1.27-1.92)
Non-small cell lung cancer	3.23 (3.08-3.39)	1.59 (1.26-2.00)	4.94 (4.07-6.00)
Small cell lung cancer			2.51 (1.97-3.20)
Prostate	Baseline	0.79 (0.57-1.10)	1.71 (1.39-2.10)
Testicular	2.49 (1.91-3.25)		2.23 (1.58-3.14)
Bladder	2.76 (2.57-2.96)	2.37 (1.86-3.0)	3.68 (2.94-4.59)
Kidney	2.17 (2.02-2.33)		4.41 (3.53-5.50)
Colon	2.45 (2.31-2.59)	1.34 (1.08-1.66)	4.28 (3.52-5.21)
Rectal			4.10 (3.34-5.03)
Stomach	4.03 (3.78-4.30)	1.67 (1.28-2.18)	4.94 (3.95-6.19)
Esophageal	4.03 (3.78-4.30)		3.86 (3.03-4.91)
Pancreatic	6.42 (5.98-6.90)	2.89 (2.21-3.77)	9.23 (7.54-11.30)
Biliary	4.38 (3.84-4.98)	1.92 (1.39-2.66)	6.43 (4.79-8.62)
Liver	1.84 (1.70-2.00)	2.13 (1.61-2.82)	6.68 (5.25-8.49)
Neuroendocrine	1.97 (1.78-2.18)	1.06 (0.69-1.62)	
Ovarian	2.93 (2.35-3.61)	1.50 (1.21-1.85)	5.52 (4.44-6.86)
Uterine			3.68 (2.91-4.65)
Cervical			3.74 (2.88-4.86)
Head & neck	1.32 (1.24-1.41)	0.65 (0.47-0.89)	
Sarcoma	2.82 (2.46-3.23)	1.41 (0.99-1.99)	
Melanoma	1.38 (1.26-1.52)	1.40 (0.72-2.74)	Baseline
Brain	5.65 (4.96-6.44)		9.11 (7.19-11.54)
Endocrine	1.05 (0.90-1.22)	0.34 (0.16-0.72)	
Myeloma	1.72 (1.57-1.87)	0.93 (0.57-1.51)	5.66 (4.46-7.19)
Aggressive NHL	2.65 (2.43-2.89)		4.61 (3.75-5.67)
Indolent NHL	1.38 (1.26-1.51)	1.39 (1.09-1.76)	
Hodgkin	2.00 (1.68-2.38)		5.73 (4.24-7.74)
ALL	4.98 (3.71-6.68)		
AML	2.10 (1.82-2.41)		
CLL	0.77 (0.68-0.87)	0.86 (0.56-1.32)	2.76 (2.17-3.50)
CML	0.57 (0.49-0.66)		
MDS	0.76 (0.66-0.87)		
Cancer stage			
Stage I	Baseline	Baseline	Baseline
Stage II	1.47 (1.41-1.54)	1.87 (1.49-2.35)	
Stage III	1.88 (1.80-1.97)	2.68 (2.17-3.30)	2.34 (2.19-2.50)
Stage IV	2.78 (2.68-2.90)	3.89 (3.17-4.78)	4.00 (3.74-4.27)

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morphism genetic risk score.[28] Three risk scores expanded on additional clinical risk factors.[25,26,29] In external validation studies, the original Khorana score and most of the earlier adaptations had an area under the curve (AUC) of 0.57-0.64.[15,16,29-32] The two recently published risk prediction scores had improved AUC of 0.66-0.68 in modified Vienna CAT and 0.68-0.71 in EHR-CAT.[16,27,29,30] The modified Vienna CAT from Pabinger *et al*. relied on cancer type and D-dimer nomogram with relatively high degree of accuracy.[27] The EHR-CAT from Li *et al*. was a modern adaptation of the Khorana score. It was derived and validated in elec-

Table 3. Continued from previous page.

	Martens	da Costa	Mulder
Location	**US**	**US**	**Denmark**
Cancer treatment			
No treatment	Baseline	Baseline	Baseline
Chemotherapy	1.44 (1.40-1.49)	1.92 (1.68-2.18)	2.16 (1.98-2.36)
Immune checkpoint inhibitor	1.49 (1.22-1.82)	1.29 (0.67-2.50)	1.78 (1.02-3.10)
Targeted therapy	1.21 (1.13-1.30)	1.07 (0.78-1.47)	
Hormone therapy	1.20 (1.12-1.28)	1.89 (0.94-3.79)	0.95 (0.81-1.12)
Older age	1.02 (1.01-1.04) per year	1.16 (1.01-1.34) For 65+ vs. <65	Increasing per decade
Male sex	1.15 (1.06-1.24)	1.04 (0.94-1.16)	1.02 (0.97-1.06)
Race			
Non-hispanic white	Baseline	Baseline	
Non-hispanic black	1.23 (1.19-1.27)	1.15 (1.00-1.33)	
Non-hispanic asian pacific islander	0.84 (0.76-0.93)	0.58 (0.44-0.77)	
Hispanic	1.04 (0.98-1.10)	0.86 (0.75-0.99)	
Area of deprivation index			
1st quartile	Baseline	Baseline	
2nd quartile	0.96 (0.92-1.00)	1.01 (0.88-1.15)	
3rd quartile	0.95 (0.91-0.99)	1.07 (0.94-1.22)	
4th quartile	0.94 (0.90-0.98)	0.94 (0.82-1.08)	
BMI 35+	1.27 (1.23-1.31)	1.29 (1.12-1.49)	
VTE history	2.75 (2.65-2.86)	1.59 (1.13-2.25)	8.24 (7.81-8.69)
Recent hospitalization	1.17 (1.13-1.21)	1.54 (1.39-1.70)	
Immobilization or paralysis history	1.20 (1.08-1.35)		
Comorbidity score	0.97 (0.95-1.00)	0.98 (0.87-1.10)	0.79 (0.67-0.94)

All numbers in this table represent hazard ratios from cause-specific Cox regression models. Only risk factors present in multiple studies are shown here. US, United States; NHL, non-Hodgkin lymphomas; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous

Table 4. Racial Disparities for cancer-associated thrombosis observed in the United States.

Author	Population	N	Years	Non-hispanic white	Non-hispanic black	Hispanic	Asian/Pacific islander
Raskob JTH 2022	Oklahoma county, Oklahoma	Incidence rate	2012-2014	32.5/100,000-py	40.9/100,000-py	5.6/100,000-py	7.7/100,000-py
Martens JAMA Open 2023	Veterans, USA	434,203	2006-2021	Baseline	1.23 (1.19-1.27)	1.04 (0.98-1.10)	0.84 (0.76-0.93)
da Costa AJH 2021	Harris county, Texas	15,342	2011-2020	Baseline	1.15 (1.00-1.33)	0.86 (0.75-0.99)	0.58 (0.44-0.77)
Mahajan Semin Thromb Hemost 2019	California cancer registry, California	942,109	2005-2017	Baseline	1.43 (1.37-1.49)	0.93 (0.89-0.96)	0.62 (0.59-0.65)

Py, patient-year.

tronic health record data and composed of cancer type (4 categories), advanced stage, cancer treatment (chemo/immune *vs*. targeted/endocrine), pre-treatment leukocyte, hemoglobin, and platelet count, body mass index, VTE history, paralysis/immobilization history, recent hospitalization, and Asian race (https://dynamicapp.shinyapps.io/EHR-CAT/).[29] Inherently, clinical risk prediction score is a trade-off between complexity and accuracy.[33] Given the rapid development in artificial intelligence and health informatics, it is conceivable that these models will be soon incorporated into clinical decision-support tools to aid decision-making.

Recurrence risk after cancer-associated thrombosis diagnosis

After the first CAT event, the risk of VTE recurrence remains elevated despite anticoagulation treatment. In 4 randomized controlled trials comparing DOAC *vs*. low-molecular-weight heparin (LMWH), the pooled 6-month recurrence was 5.6% in the DOAC arm and 8.3% in the LMWH arm.[34] The exact recurrence rate in epidemiology studies is difficult to assess due to the lack of a validated algorithm for the recurrent VTE outcome. Many studies have utilized a combination of ICD codes at the principal inpatient discharge diagnosis position, anticoagulant medication interruption/resumption, and/or imaging procedure codes. However, no study to date has presented validation of such algorithms in cancer patients. Despite potential ascertainment bias, the 12-month VTE recurrence rate was reported to be 6.7%-15.3% in 6 large cohort studies (Table 5).[5,22,35-38] All except one of the studies were performed before the DOAC era. Reliable longer-term VTE recurrence data beyond 1-year are lacking.

Mortality risk after cancer-associated thrombosis diagnosis

The impact of CAT on the mortality risk in cancer patients remains another challenging topic. Since VTE occurrence has strong associations with aggressive cancer and advanced staging, it is inevitably correlated with worse survival. To account for confounding and selection bias, Sorensen *et al*. performed a retrospective cohort study using the Danish cancer registry to compare cancer patients with concurrent cancer and VTE diagnosis *vs*. those with cancer but no VTE after matching on age, sex, cancer type, and stage. The authors found that 1- and 5-year cumulative incidence for mortality was 68% and 84% in the CAT cohort *vs*. 38% and 67% in the non-CAT cohort (HR 4.34, 95% CI 3.95-4.78). Among

Table 5. Incidence of cancer-associated thrombosis recurrence in selective population studies.

Author	Location	Design	N	Year	Study population	VTE definition	Recurrence risk/rate
Raskob JTH 2022	Oklahoma county, Oklahoma	Surveillance study	3,422	2012-2014	Oklahoma county residents with cancer and VTE	Inpatient and outpatient PE and DVT (ICD code + imaging)	12 months: 12.5%
Cohen Thromb Haemost 2017	UK clinical practice research datalink	Retrospective cohort	6,592	2001-2011	UK residents with "active" solid + heme cancer and VTE	Inpatient PE, LE-DVT, UE-DVT (excluding cerebral and abdominal vein thrombosis) (ICD code + chart review)	6 months: 7.4% 12 months: 9.2%
Ording Int J Cardiol 2023	Danish cancer registry	Retrospective cohort	34,702	2003-2018	Danish residents with active cancer and first-time diagnosis of VTE	Inpatient and outpatient PE and DVT (ICD code + imaging)	6 months: 5.1% 12 months: 6.7%
Lecumberri Thromb Haemost 2022	Computerized registry of patients with venous thromboembolism (RIETE) registry	Retrospective cohort	16,694	2001-2020	Spanish residents with cancer and VTE	Inpatient and outpatient symptomatic PE, LE-DVT, UE-DVT (imaging)	10.5/100-py at median 150d in solid cancers 7.7/100-py at median 127d in heme cancers
Hwang Clin Exp Thromb Hemost 2021	Korean health insurance review and assessment	Retrospective cohort	19,725	2004-2013	Korean residents with cancer and VTE	Inpatient and outpatient PE, LE-DVT (ICD code + medication)	7.1% at median 1.6 years
Khorana AJH 2019	Truven health MarketScan database	Retrospective claims database	13,804	2013-2016	Commercially-insured patients with cancer and VTE	Inpatient primary discharge diagnosis (ICD code only)	12 months: Rivaroxaban: 11.3-13.3% LMWH: 14.7%-15.3% Warfarin: 11.6-13.3%

VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; ICD, International Classification of Diseases; LE-DVT, lower extremity deep vein thrombosis; UE-DVT, upper extremity deep vein thrombosis; py, patient-year.

patients with CAT onset after cancer diagnosis, the 1- and 5-year cumulative incidence for mortality was 45% (HR 3.48, 95% CI 3.37-3.60) and 69% in the CAT cohort (HR 2.57, 95% CI 2.50-2.63).[39] Similarly, Mahajan *et al*. reported that the adjusted hazard ratios ranged from 1.89 to 4.79 across various cancer types when the onset of CAT was treated as a time-varying covariate to account for immortal time bias.[11]

Future direction

Significant advances have been made in the past decade to better elucidate the epidemiology, prevention, and management of CAT. Nonetheless, despite improved risk prediction scores, randomized trials, and guideline recommendations, most oncologists are not aware of the available tools.[40] Future areas of research include some of the following: i) hybrid implementation projects aimed at physician and patient education; ii) integration of risk prediction scores into electronic health records with longitudinal real-time updates; iii) development and validation of artificial intelligence-assisted but transparent VTE risk models; iv) incorporation of comprehensive plasma biomarkers using commercially available assays to measure proteomics or cell-free DNA; v) development of validated natural language processing algorithms for recurrent VTE to ascertain short- and long-term epidemiology of VTE recurrence.

Conclusions

In summary, the 12-month incidence of CAT among patients with unselected cancers in the modern era is approximately 3-5% in Western countries (9-fold increase *vs*. matched non-cancer population) and 1% in eastern Asian countries; although the risk increases to 6-8% in patients with selectively advanced cancers requiring systemic therapy (20-fold increase *vs*. matched non-cancer population). Despite improvement in anticoagulation usage and adherence, recurrence risk remains high at 5-8% at 6 months and 7-15% at 12 months. The most important clinical predictors of CAT development are cancer type, cancer stage, cancer treatment, prior VTE history, prolonged hospitalization and immobilization, and obesity. Several clinical risk prediction scores for CAT utilizing the initial Khorana score backbone have been developed and externally validated, though more studies are needed to ensure adequate implementation and usage of these models. We encourage multidisciplinary collaborations between hematologists, oncologists, epidemiologists, and data scientists to ensure the adoption of personalized VTE risk assessment in routine oncologic care.

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