Bleeding Risk in Cancer Patients with Acute Venous Thromboembolism in Alberta, Canada

by

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ABSTRACT

Background: Cancer-associated venous thromboembolism (VTE) is associated with significant morbidity and mortality. Cancer patients are at higher risk of VTE recurrence despite anticoagulation and bleeding complications while on anticoagulation. There are some risk factors of bleeding specific to cancer patients. We sought to assess the bleeding rates in cancer patients within one year of acute VTE over a 10-year period in Alberta, Canada and to identify whether cancer site affects these rates.

Methods: Our population included all adult patients of Alberta diagnosed primarily with acute VTE between April 2002 and March 2012. We categorized patients into cancer and non-cancer population and we measured the bleeding rates in both groups then stratify by cancer site within the cancer group. We used purposeful logistic regression to calculate odds ratios and identify some predictors of bleeding.

Results: Of 5,158 cases of cancer-associated VTE, 127 patients (2.46%) developed bleeding within one year of VTE event compared to 441 of 26,498 cases in the non-cancer group (1.66%) ($p<0.0001$). The main site of bleeding was gastrointestinal (91.34%) and the main site of cancer associated with higher bleeding risk was gastrointestinal cancer (OR 2.60; $p=0.03$). In terms of predictors of bleeding, the following risk factors contributed to the highest risk of bleeding: previous bleeding episode (OR 8.01; $p<0.001$), anemia (OR 5.72; p'0.001), liver disease (OR 2.2; $p<0.001$), alcohol use (OR 1.97; $p<0.001$) and hypertension (OR 1.28; $p=0.014$).

Conclusion: The bleeding risk is higher in cancer-associated VTE and it differs according to the cancer site. Bleeding is a big concern in cancer population and more efforts should be made to find the safest anticoagulant modality in each cancer type.

Dedicated

to my inspiring

Mom and Dad

and to the loves of my life

Ghassan, Ali and Julia

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CHAPTER 1

INTRODUCTION

1.1. INTRODUCTION TO VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE) is defined as clot formation within a vein resulting in vein occlusion and subsequently diminishes venous return[1]. Venous thrombi can occur in the deep veins of the extremities, thus the term deep vein thrombosis (DVT). These thrombi can be dislodged and can reach the pulmonary arteries through the right side of the heart causing pulmonary embolism (PE). Together both DVT and PE are referred to as VTE.[2] The causes of VTE are divided into inherited and acquired.[3] The main mechanism of thrombus formation is described by the Virchow's triad: venous stasis, vascular endothelial injury and hypercoagulable state.[1, 4]

1.2. INCIDENCE

The annual incidence of VTE has undergone a significant increase with the introduction of diagnostic tools in the last 2 decades such as D-dimer and computed tomographic pulmonary angiography (CTPA).[5, 6] The incidence of PE, for instance, has increased by 81% from 62.1 to 112.3 per 100,000 after the introduction of CT-PA in 1998. Thereafter, the incidence of VTE tended to be somewhat steady. The Worcester study conducted between 1999 and 2003[7] and the AB-VTE study covering the period between 2002 and 2012[8] showed no significant change in incidence rates over time. Most of the studies reported an annual incidence rate in the range of 0.75 to 2.69 per 1000 persons.[7-11]

1.3. RISK FACTORS OF VTE

The main pathophysiology of VTE is explained by the three components of the Virchow's triad: endothelial injury, venous stasis or immobility and hypercoagulable state.[4] Subsequently, VTE is categorized into either unprovoked, which refers to the lack of predisposing factor, or provoked. The latter also includes a separate entity caused by the presence of malignancy called cancer-associated VTE.[12] This notion of provoked versus unprovoked was first introduced by Kearon to replace the previously used terms of idiopathic and secondary VTE in the 1980s.[13, 14] This classification is of great importance because it allows for identification of risk factors when present and therefore the ability to treat them which results in avoiding death and recurrence of VTE.[15] It will also affect the duration of anticoagulation.[14, 16]

The predisposing etiological factors for VTE include intrinsic factors such as older age (>70 years old), gender, obesity, previous VTE and hereditary thrombophilia, and acquired or extrinsic factors such as malignancy, cancer chemotherapy, surgery, hospitalization, immobility, pregnancy and puerperium.[17, 18]

1.4. CANCER-ASSOCIATED VTE

Cancer has been described as a risk factor of VTE by Trousseau in the nineteenth century known as Trousseau's syndrome.[19, 20] The incidence of VTE depends highly on the type of cancer and the stage of the disease. It has been reported to be higher in metastatic cancers at the time of diagnosis.[21] The risk of developing VTE is 4.1 higher in cancer patients than in non-cancer patients.[18] About 20% of patients with cancer will develop VTE.[2] VTE in cancer patients is associated with a significant risk of mortality and morbidity. A Danish study showed that cancer patients with VTE are at about twice higher risk of dying at 15 years of follow-up than

those without VTE.[22] Khorana et al also reported a higher mortality rate in hospitalized neutropenic cancer patients diagnosed with VTE compared to those who were not.[23] Thromboembolism, whether arterial or venous, comes second as a leading cause of death after cancer progression.[24]

1.4.1. Pathophysiology of VTE in cancer patients

A hypercoagulable state characterizes most of cancer patients. The pathogenesis is thought to be multifactorial involving tumor-specific factors, anatomic factors, patient-specific factors and therapy-associated factors. The latter two factors will be discussed in the "predictors of VTE in cancer patients section". (Table 1.1)

Table 1.1. Potential Risk Factors for VTE in Patients With Active Cancer[25]

Patient-Related Factors	Cancer-Related Factors	Treatment-Related Factors	Other risk factors
Demographics: age, sex, race	Primary site of cancer	Chemotherapy, hormonal, and biological therapy	Leukocyte count
Performance status	Histology	Surgery	Platelet count
Prior history of VTE	Stage	Indwelling catheters	Anemia
Obesity	Time interval from cancer diagnosis	Supportive measures such as erythropoietin-stimulating agents, other growth factors	Thrombophilia
Number of chronic medical comorbidities		Hospitalization	

Factors secreted by tumor cells, namely tissue factor and cancer procoagulant activate the coagulation cascade. Tissue factor, a surface protein expressed on certain normal and cancerous cells, activates the extrinsic coagulation pathway.[26, 27] Tissue factor is not only expressed on cells surface, it is also associated with what is called tumor-derived tissue factor-bearing

microparticles resulting in the dissemination of fibrin through binding to the formed thrombus, therefore increasing the risk of thromboembolic event in the setting of cancer.[28]

With regards to cancer procoagulant, it is a cysteine protease that is thought to be contributing to the mechanism of hypercoagulability through direct activation of factor X.[29] In addition, cytokines released by tumor cells and platelet interaction with tumor cells play a role in clot formation and hypercoagulability.[30, 31]

The presence of tumor-specific agents such as polyphosphate, which activates the intrinsic coagulation pathway, and MET-oncogene is also associated with thrombosis.[32, 33]

The risk of VTE is increased by certain anatomic factors such as direct infiltration or external compression of large vessels; to cite, the infiltration of inferior vena cava by renal cell carcinoma or compression of deep veins of the legs by large abdominal or pelvic masses.[34-36]

1.4.2. Predictors of VTE in cancer patients

Most of cancer diagnoses are usually made before VTE occurrence.[22] However some reports identified malignancy after the VTE event.[37-39] Given the higher risk of death reported in cancer patients with VTE, it is of great importance to identify the risk factors that also contribute to the association between cancer and VTE. First, VTE events are associated with cancer site: most commonly lung, pancreas, colon and rectum, kidney and prostate.[22] Second, the development of VTE within one year of cancer diagnosis is proportionally correlated with the initial cancer stage. Wun and White in their study on the risk factors and epidemiology of VTE and cancer patients found that the incidence of VTE was significantly lower in local stage melanoma, bladder, and uterine cancer when compared to the metastasized stage of the same cancer types.[40] Third, major surgical procedures double or even quadruple the incidence of VTE

in cancer patients compared to the general population.[41] Fourth, patient comorbidities are also determinant factors in the tendency to thrombosis in cancer patients.[42] Older age, obesity, previous history of VTE, the presence of inherited thrombophilia, immobility, longer hospital stay and metastatic disease predict the development of VTE in cancer patients.[43] Finally, some antineoplastic agents increase the risk of VTE by 4.5 to 6-folds.[18] As examples, thalidomide and lenalidomide are newer agents associated with VTE.[44, 45] Other thrombogenic agents include cisplatin and 5-fluorouracil used in treating gastrointestinal, cervical and lung cancers,[46, 47] as well as asparginase used in treating acute lymphoblastic leukemias.[48]

1.4.3. Risk assessment of VTE in cancer patients

The risk of VTE is increased in cancer patients. Several scores have been established to assess the risk of developing VTE in cancer patients. The main goal of these scores is to identify if primary thrombophylaxis is indicated in individuals diagnosed with cancer especially those receiving chemotherapy to prevent thromboembolic event.[25, 49] The Khorana score is the most popular one used in ambulatory cancer patients on chemotherapy. It is a simple model that basically consists of five parameters, both clinical and laboratory, including the cancer site, prechemotherapy platelet and leukocyte counts, hemoglobin level and body mass index (Table 1.2).[50] This score was then validated to include high risk tumours such as brain, myeloma and kidney.[51, 52] Additional chemotherapeutic agents like platinum and gemcitabine were then studied forming the PROTECHT score or prophylaxis of thromboembolism during chemotherapy.[53, 54] The latter is a modified version of the Khorana score that takes into consideration certain types of chemotherapy and allows for risk stratification of VTE in cancer patients. The clinical application of this score is still under investigation.

Table 1.2. Khorana score for chemotherapy-associated VTE[50-52]

Risk factor	Points	Khorana score points
Site of primary tumor		**0 : low** **1 to 2 : intermediate** **≥3 : high**
Very high risk (stomach, pancreas)	2	
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1	
All other sites	0	
Prechemotherapy platelet count ≥350,000/microL	1	
Hemoglobin level <10 g/dL or use of erythropoiesis-stimulating agents	1	
Prechemotherapy white blood cell >11,000/microL	1	
Body mass index (BMI) ≥35 kg/m^2	1	

1.4.4. Treatment of VTE in cancer patients

VTE is treated differently based on whether the patient has cancer or not as established by the CHEST guidelines. However, there are no differences in the indication and contraindications to treatment of VTE. Direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, apixaban and edoxaban are increasingly becoming the mainstay of treatment of VTE in the general population, favored over vitamin K antagonists (VKA) and low molecular weight heparin (LMWH). However, the recommendations are different for VTE and cancer. The treatment of VTE and cancer consists of LMWH over VKA, dabigatran, rivaroxaban, apixaban and edoxaban. Extended anticoagulation therapy is also recommended over 3 months therapy in the cancer population. The use of LMWH over VKA in cancer-associated thrombosis is preferred for many reasons: higher efficacy of LMWH in cancer population, higher recurrence rate of VTE with VKA, better tolerance of LMWH if anorexia or vomiting and easy to stop if there is any risk of bleeding secondary to thrombocytopenia or invasive procedures.[55] Newer data exploring the use of DOACs in cancer associated thrombosis is emerging and while efficacy

appears similar to LMWH, major bleeding particularly gastrointestinal (GI) and genitourinary (GU) in patients with GI and GU cancers is a concern.[56]

Anticoagulation treatment aims at preventing recurrence and extension of thrombi/emboli taking into consideration the risk of bleeding with anticoagulant use.[57]

1.4.5. Complications of VTE in cancer patients

The main complications of VTE consist of the risks of recurrence and bleeding. In cancer patients, the risk of VTE recurrence is higher than the general population despite the use of anticoagulant therapy posing high morbidity and mortality risks.[58] VTE recurrence occurs in about 7 to 16 percent of cases.[59-62] As for bleeding, the risk is also higher among cancer patients compared to other patients without cancer. The bleeding incidence in cancer ranges between 6.5 and 18 percent.[57, 63, 64] Bleeding complication occurs more frequently during the first month and is not related to subtherapeutic or supratherapeutic anticoagulation. The severity of cancer at diagnosis also determines the complication risk.[63] Therefore treatment options are still under study to find the safest approach according to the extent of cancer and the balance between recurrence and bleeding risks. The mortality risk from bleeding in cancer patients with VTE was reported in the RIETE registry at around 29%. The most reported sites of bleeding are the gastrointestinal and the genitourinary tracts as well as cerebral bleeding.[65] That being said, it is important to determine the factors that may contribute to the risk of bleeding. Cancer patients have additional risk factors for bleeding to those of the general population without cancer. The common known risk factors for bleeding in the general population include older age (>65 years), higher intensity anticoagulation, previous gastrointestinal bleeding, thrombocytopenia and bleeding diathesis such as cirrhosis with elevated INR.[66] The RIETE registry identified risk factors for bleeding specific to the cancer population including recent bleeding, creatinine

clearance <30 ml/min, metastatic-stage cancer, body weight less than 60 kg and recent immobility ≥4 days.[64, 65] Whether cancer or cancer type significantly influences risk for bleeding is not known.

1.5. OBJECTIVES

Current data on the risk of bleeding in cancer patients are very limited.[64, 65] To our knowledge, there is no cohort study in Canada using the administrative health data that has focused mainly on the complications among cancer subgroups in VTE. Additionally, an AB-VTE registry has been created in Alberta that looked at the epidemiology of VTE in Alberta. It studied the trends in incidence and mortality rates in VTE patients as well as the trends in admission rates and length of stay of patients with VTE during the period of 2002 to 2012.[8, 67, 68] We thought of focusing our study on the cancer subgroup of the AB-VTE database. The aim of this study is to provide current population-based data about the rates of bleeding in cancer patients with VTE, to stratify the bleeding risk by cancer types and to describe the patients at risk of bleeding. This information will help the health services in Alberta and therefore Canada to have a better understanding of fatal hemorrhagic complications in cancer patients, hence to identify areas of higher need of medical advancements.

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CHAPTER 2

Bleeding Risk in Cancer Patients with Venous Thromboembolism

2.1. ABSTRACT

Background: Cancer-associated thrombosis is associated with significant morbidity and mortality. Cancer patients are at higher risk of both VTE recurrence despite anticoagulation and bleeding complications while on anticoagulation. There are some risk factors of bleeding specific to cancer patients established by some studies. We sought to assess the bleeding rates in cancer patients within one year of acute VTE over a 10-year period in Alberta, Canada and to identify whether cancer site affects these rates.

Methods: Our population included all adult patients of Alberta diagnosed primarily with acute venous thromboembolism between April 2002 and March 2012. We categorized patients into cancer and non-cancer population and we measured the bleeding rates in both groups then stratify by cancer site within the cancer group. We used purposeful logistic regression to calculate odds ratios and identify some predictors of bleeding.

Results: Of 5,158 cases of cancer-associated VTE, 127 patients (2.46%) developed bleeding within one year of VTE event compared to 441 of 26,498 cases in the non-cancer group (1.66%). The main site of bleeding was gastrointestinal (91.34%) and the main site of cancer associated with higher bleeding risk was gastrointestinal cancer (OR 2.60; p=0.03). In terms of predictors of bleeding, the following risk factors contributed to the highest risk of bleeding: previous bleeding episode (OR 8.01; p<0.001), anemia (OR 5.72; p<0.001), liver disease (OR 2.2; p<0.001), alcohol use (OR 1.97; p<0.001) and hypertension (OR 1.28; p=0.014).

Conclusion: The frequency of bleeding was higher in cancer-associated VTE and was different across cancer sites. Bleeding is still a big concern in cancer population and more efforts should be made to find the safest anticoagulant modality to each cancer type.

Keywords: AB-VTE, Pulmonary Embolism, Deep Vein Thrombosis, Cancer, Cancer Site, Bleeding, Predictors.

2.2. INTRODUCTION

Trousseau was the first to describe the correlation between cancer and venous thromboembolism (VTE) in the nineteenth century. Migratory phlebitis as a common presentation of malignancy is currently referred to as Trousseau's syndrome.[1, 2] In patients without chemotherapy, cancer increased the risk of VTE by 4.1 folds.[3] A higher risk of morbidity and mortality is also associated with VTE in cancer patients.[4, 5] Furthermore, many studies have reported a greater incidence of VTE complications in cancer patients that exceed those seen in the general population.[6-8] These complications include a risk of recurrence of VTE despite anticoagulation and a risk of bleeding while on anticoagulation. The reason behind this is the presence of certain risk factors that are specific to cancer patients, in addition to those contributing to VTE in non-cancer patients, namely the primary site of cancer, the stage of cancer at time of diagnosis, the time elapsing between cancer diagnosis and occurrence of VTE and chemotherapy treatment.[3, 9-11] That being said, anticoagulation strategies for treatment and prevention of VTE in cancer population as well as the duration of treatment, are updated frequently to find the safest and most effective regimen capable of balancing the benefits of anticoagulation in preventing recurrence with the risks of bleeding. The 2016 CHEST guidelines recommend the use of low molecular weight heparin (LMWH) over vitamin K antagonists (VKA) and direct oral anticoagulants such as dabigatran, rivaroxaban, apixaban and edoxaban.[12] Recently, edoxaban was shown to have higher risk of bleeding in cancer patients when compared to dalteparin.[13] Other trials studying the safety and efficacy of direct oral anticoagulants in cancer-associated thrombosis are still ongoing.

Despite the valuable information provided by the RIETE registry,[8]current data on bleeding rates among cancer patients with acute VTE are still limited. In particular, how cancer type influences

risk for bleeding complications while anticoagulated is not known. In this population-based study, we used administrative health databases in the province of Alberta, Canada over a 10-year period from 2002 to 2012. The aim of this study is to measure the bleeding rates in cancer patients with new-onset VTE and to stratify the risk by cancer type.

2.3. METHODS

2.3.1. Study design and data source

This provincial retrospective cohort study was conducted using the Alberta-Venous Thromboembolism (AB-VTE) database that is established by linking five administrative health databases in Alberta, Canada. The databases consist of: 1) the ambulatory care database includes both the emergency department and the outpatient clinic visits (April 1, 2002 to March 31, 2014); 2) the hospital inpatient discharge database (April 1, 2002 to March 31, 2014); 3) the physician claims database (April 1, 2002 to March 31, 2014); 4) the population registry database (April 1, 2002 to March 31, 2014); and 5) Vital Statistics (i.e., death registry from January 1, 2002 to December 31, 2012). This study was approved by the University of Alberta Health Research Ethics Board. The ambulatory care database contains up to 10 diagnostic and procedure codes, whereas the hospital inpatient discharge database contains up to 25 diagnostic and 20 procedure codes.

2.3.2. Study population

The study involved all patients who had incident acute pulmonary embolism and/or deep vein thrombosis, as per ICD diagnostic codes for VTE anytime between 2002 and 2012. These individuals are all residents of the province of Alberta, aged 18 years or older. We included the study subject from the time of diagnosis to either the time of death or the end of the study in March 31, 2012, whichever occurred first. Acute DVT was defined by the following codes: ICD-

9 CM: 451.1. 451.2, 451.8, 451.9, 453.2, 453.8, or 453.9; ICD-10: I80.2, I80.3, I80.1, I82.8, I80.9, I82.9, I80.8, O22.3, O22.9, or O87.1. Whereas, the diagnosis of acute PE was defined as follows: ICD-9 CM: 415.0 and 415.1 and ICD-10: I26.9, I26.0. If both events were present simultaneously, the patient will be considered as having PE. We used a washout period of 2 years to include only the incident cases. The detection of acute VTE was made by the presence of one of the previous ICD codes coupled with an imaging code for VTE within a 7-day timeframe. The date of diagnosis is considered either the date of imaging study or the date of admission for patients based respectively on whether they were detected in the ambulatory care/physician claim databases or the hospital inpatient discharge database. This algorithm has a a positive predictive value of 83.1% through validation against chart audits in Alberta.[14]

2.3.3. Study Outcomes and Covariates

The primary outcome studied was the bleeding risk in cancer-associated VTE. Cancer-associated VTE was defined as the presence of a diagnostic code of any cancer within a year prior to VTE excluding skin cancers. Bleeding is defined as the first health encounter to the hospital or emergency department with a primary or secondary diagnosis of bleeding using the following ICD-10 diagnostic codes. GI bleeding: K25.0, K25.2, K25.4, K25.6, K26.2, K26.4,26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K92.0, K92.1, I85.0, I98.3, IC bleeding: I60, I61, I62, I69.0, I69.1, I69.2, S06.4, S06.5, S06.6, GU bleeding: N02, R31, N89.7, N92.4, N93, N95.0,O20, O46, O71.9, O72, Airway bleeding: J94.2, R04 and Hemarthrosis: M25.0. We calculated bleeding rates at 12 months after the diagnosis of cancer-associated VTE. We defined comorbidities as being present in the ambulatory care or inpatient databases within one year of onset of VTE. Recent bleeding was also considered to be present if the previous diagnostic codes for bleeding were recorded at any time in the past year

preceding the VTE event. Other risk factors like major surgery, major trauma, hip fracture within the previous 3 months, ongoing or recent pregnancy (within 3 months from delivery) and hospitalization for other causes for more than 3 days in the last 3 months were identified. We used a 2-year washout period for all defined variables.

2.3.4. Statistical analysis

We reported continuous variables as means and standard deviation and categorical variables as frequencies and percentages in the description of patient demographic and clinical characteristics. We used Chi-square and Fisher exact tests to test the proportions between cancer and non-cancer groups. We calculated the odds ratios and 95% confidence intervals of bleeding in patients with cancer according to the site of cancer and the presence of metastases. For that purpose, we used purposefully selected multivariate logistic regression models for which all necessary assumptions have been met. We adjusted models for confounders and we identified some predictors of bleeding.

A 2-sided P-value <0.05 was considered statistically significant. Statistical analyses were performed using Stata (Stata Statistical Software: Release 13; StataCorp LP, College Station, TX).

2.4. RESULTS

2.4.1. Patient characteristics

During the study period from 2004 to 2012, a total of 5,158 out of 31,656 cases of acute VTE were cancer-associated (16.29%). 3,440 of 23,015 (14.95%) patients in the DVT group and 1,718 of 8,641 (19.88%) patients in the PE group had cancer. Of these 5,158 cancer patients diagnosed with first time VTE, 127 patients (2.46%) developed bleeding at some point during

one year after the diagnosis of VTE. Whereas, 441 of the remaining 26,498 cases of non-cancer associated VTE (1.66%) developed bleeding complication during the same period. The mean age of bleeding was 62.28 ± 1.29 years and 60.96 ± 0.91years in the cancer and non-cancer groups respectively ($p<0.0001$). 37.01% of bleeding cases in cancer patients were females compared to 56.46% in the non-cancer patients ($p<0.0001$). Cancer patients had a higher frequency of risk factors than the non-cancer patients, such as recent hospitalization for more than 3 days, major surgery, anemia and thrombocytopenia. The frequency of previous episodes of major bleeding was insignificantly higher in the cancer group (18.90% versus 12.70% with a p=value of 0.077). The baseline demographic characteristics, risk factors and comorbidities of study patients are summarized in Table 2.1.

2.4.2. Bleeding in different cancer sites

The incidence rate of bleeding was different among the various sites of cancer (Table 2.2). Gastrointestinal cancers were associated with the highest rate of bleeding (3.96%). The incidence rates of bleeding among this cancer group were distributed as follows: 7.78% for gastric cancer followed by cancer of the small intestine (4.76%) then hepatobiliary and pancreatic cancer (4.69%) and finally colorectal cancer (3.09%). Cancers of the kidney, bladder and prostate came next and their incidence of bleeding was 3.48%. Endometrial cancer followed with a bleeding rate of 3.06%. The incidence rates of bleeding in lung cancer and breast cancer were respectively 1.27% and 0.99%.

The severity of cancer was also associated with high rates of bleeding. Among cancer patients who bled, 28.35% were found to have metastatic disease. The incidence rate of bleeding in metastatic cancer was 2.1%, non-significantly higher than that of non-metastatic cancer (1.78%), p=0.328.

Table 2.2 also reports the odds ratios of bleeding in patients with cancer in comparison to those without cancer stratified by cancer site after adjusting for confounders. The odds of bleeding in patients with cancer of the small intestine is about three times non-significantly higher than the odds in those without cancer (OR 2.97, 95% CI:0.37-23.79). Gastric cancer was associated with 2.6 times significantly higher odds of bleeding compared to the non-cancer population (OR 2.6, 95% CI: 1.09-6.99). Cancers of the kidney, bladder and prostate share with hepatobiliary and pancreatic cancer the same probability of bleeding (OR 1.46). Surprisingly, lung and breast cancers have non-significant lower odds of bleeding than those free of cancer (OR 0.66 and 0.64 respectively). Colon cancer patients had 1.13 times higher odds of bleeding. With regards to the stage of cancer metastatic disease was associated with higher risk of bleeding (OR 2.87, 95% CI 0.54-15.18).

2.4.3. Sites of bleeding

Bleeding rates differ according to the site of bleeding. Table 2.3 shows the different incidence rates of bleeding in cancer and non-cancer associated VTE according to the bleeding site. The highest incidence rates of bleeding occurred in the gastrointestinal tract in both cancer and non-cancer patients with 91.34% and 92.29% respectively (p=0.046). Airways bleeding had an incidence rate of 6.3% in cancer patients and 2.72% in non-cancer patients. With regards to intracranial bleeding, it occurred less frequently in patients with cancer in about 2.36% compared to 4.31% in patients without cancer (p<0.001). Genitourinary bleeding did not occur in cancer patients but occurred in 0.68% of patients without cancer.

2.4.4. Other predictors of bleeding

Our multivariate comparison of risk factors between cancer and non-cancer patients showed that some risk factors are associated with a higher risk of bleeding as follows: recent

episode of bleeding (OR 8.01; p<0.001), anemia (OR 5.72; p'0.001), liver disease (OR 2.2; p<0.001), alcohol use (OR 1.97; p<0.001) and hypertension (OR 1.28; p=0.014).

2.5. DISCUSSION

The data available on bleeding complications in cancer patients and specifically stratified by cancer site is very limited. Our cohort study of patients with cancer-associated VTE in Alberta demonstrates that bleeding occurred more frequently in patients with cancer as compared to patients without cancer (2.46% versus 1.66 percent; p<0.0001). Our findings are in keeping with the literature. Cancer patients are known to have higher risk of bleeding complications than those free of cancer.[6-8, 15] However, our bleeding rates were lower than those described in the RIETE registry and the DALTECAN trial where major bleeding accounted for about 10% of cases while on Dalteparin.[16] Findings from the RIETE registry about major bleeding in cancer patients showed that 4.1% developed bleeding during the first three months of VTE event.[11] Khorana et al also reported an all-cause bleeding rate of 17.7% in cancer patients.[17] On the other hand, the RIETE investigators reported in one study a bleeding rate of 1% in cancer patients with VTE.[8] The lower rates of bleeding in our study can be due to the possibility that our patients are less sick or they have less aggressive cancer. This is difficult to confirm with our administrative database for lack of chemotherapy and pathology data.

Our findings agree with previous studies emphasizing the effect of cancer site on bleeding outcomes.[18] The odds ratios for bleeding differed according to the cancer site. In our data, gastrointestinal cancer was associated with the highest risk of bleeding as compared to patients without cancer. In a study done at the University of Padua by Prandoni et al,[7] the risk of major

bleeding was the highest in genitourinary cancer followed by breast cancer. Gastrointestinal cancer, was associated with 1.3 times higher risk of bleeding than patients without cancer. Additionally, in a study about the clinical course of VTE based on cancer site, gastrointestinal cancer shared similar high rates of bleeding among cancer patients[18] which is in keeping with our findings. Surprisingly, lung cancer and breast cancer were non-significantly associated with lower risk of bleeding than the general population. Similarly, no fatal bleeding occurred in breast cancer patients enrolled in the RIETE registry by Monreal et al.[8] In contrast, in Mahe et al[18], lung cancer was associated with 1.8 higher risk of bleeding complication. In terms of severity of cancer, with agreement to the finding by Prandoni et al[7] that extensive cancers correlated with high bleeding rates, metastatic cancer in our study increased the risk of bleeding by 2.87 times.

In terms of site of bleeding, it was quite similar between the cancer and non-cancer group. Interestingly, we did not observe any genitourinary bleeding in our cohort of cancer patients. But as foreseeable, gastrointestinal bleeding was the most common site of bleeding in cancer patients followed by airway bleeding and intracranial bleed. Previous studies have revealed similar results.[18]

We studied the predictors of bleeding based on the common risk factors and the scores described in the literature to help assess the risk of major bleeding in anticoagulated patients. The HAS-BLED score was validated and used to weigh the risks and benefits of anticoagulation in atrial fibrillation.[19, 20] We added to these determinants of bleeding those described by the RIETE study[11] as being specific to cancer patients with VTE. In this latter study, recent bleeding, renal disease, immobility and metastases predispose cancer patients to a higher risk of bleeding. In our cohort, we found that the odds of bleeding are more than eight times higher if patients had a previous episode of bleeding. Moreover, liver disease, alcoholism, anemia and hypertension play

an important role in determining the risk of bleeding. These predictors are included in the scores described previously.[11, 19, 20]

Therefore, we believe that our findings constitute a valuable asset to the limited literature on bleeding risk in cancer patients with VTE and further raise the demand to focus on this specific subgroup of patients. These data enhance the fact that cancer patients with VTE are at higher risk of bleeding compared to their cohorts free of cancer. We also demonstrated that bleeding risk differs by cancer site. This fosters the controversial issue about the choice, intensity and duration of anticoagulation therapy in patients with cancer. This was recently highlighted in a randomized controlled trial which showed a significantly higher rate of major bleeding (particularly GU and GI bleeding) in GI and GU cancer patients taking edoxaban compared to dalteparin.[13] Therefore, efforts should be directed towards designing more interventional studies that take into consideration the cancer population in addition to the cancer site in order to find the best and safest anticoagulation strategy that can balance between their risks and benefits.

In addition to the advantages cited above, our results reflect the Albertan population as all adult residents of Alberta who were diagnosed with a first time VTE. Therefore, they can be generalized to be used by the local health authorities as a comprehensive approach to VTE complications in cancer patients that could change management strategies and patient outcomes. Moreover, our case definition of VTE was validated against chart audits in Alberta.[14]

However, our study has some limitations. First, the definition of bleeding, as described by ISTH criteria,[21] could not be applied to our case definition because of the retrospective nature of the study based on administrative health databases that lack data about some of the clinical variables included in those criteria such as fall in hemoglobin, need for transfusion and symptomatic

bleeding. Instead, our bleeding definition was mainly the first health encounter to the hospital or emergency department based on the ICD-10 codes of the commonly-known major bleeding: intracranial, gastrointestinal, genitourinary, airways and intra-articular. We opted to focus mainly on the first two diagnostic codes to ensure that bleeding was one of the most responsible diagnoses. In addition, the determination of the comorbidities and risk factors was limited by the data available. For example, anemia and thrombocytopenia were mainly based on ICD codes rather than the actual laboratory values. Another important laboratory value that we were missing is the INR. Furthermore, we were lacking information about whether the patients were on anticoagulation therapy at the time of bleeding, about the nature and length of anticoagulant therapy and whether the anticoagulation was held or stopped. We also admit that our knowledge about the extent and severity of cancer was also limited by the lack of information about histology, grade and TNM classification.

2.6. CONCLUSION

The frequency of bleeding events in cancer patients was greater than that in patients without cancer. The bleeding rates also differ according to the cancer site. Gastrointestinal cancers tend to bleed the most and the gastrointestinal tract is the most common site of bleeding. The frequency of metastatic cancer was high in bleeding cases. Despite the paucity of information about VTE complications, the general consensus is that cancer patients have higher rates of bleeding on anticoagulation and higher rates of recurrence despite anticoagulant therapy. That being said, efforts should be made to identify the risks and benefits of different anticoagulation modalities and duration of therapy on each cancer type.

Table 2.1. Patient demographic and clinical characteristics

	Cancer-associated VTE	Non-cancer associated VTE	p- value
Bleeding, n(%)	127 (2.46)	441 (1.66)	0.0001
Clinical characteristics, n(%)			
Female gender	47 (37.01)	249 (56.46)	0.0001
Mean of age, years	62.28 ± 1.29	60.96 ± 0.91	0.0001
Age groups			0.0001
18-39	4 (3.15)	72 (16.33)	
40-59	25 (19.69)	116 (26.30)	
60-79	64 (50.39)	171 (38.78)	
≥80	34 (26.77)	82 (18.59)	
Comorbidities (≤1y)			
Acute myocardial infarction	6 (4.72)	31 (7.03)	0.354
Congestive heart failure	9 (7.09)	48 (10.88)	0.209
Peripheral vascular disease	1 (0.79)	18 (4.08)	0.069
Cerebrovascular accident	8 (6.30)	24 (5.44)	0.712
Peptic ulcer disease	10 (7.87)	27 (6.12)	0.481
Liver disease	6 (4.72)	29 (6.58)	0.445
Diabetes mellitus	19 (14.96)	79 (17.91)	0.438
Renal disease	8 (6.30)	35 (7.94)	0.539
Hypertension	40 (31.50)	135 (30.61)	0.849
Connective tissue disease	3 (2.36)	16 (3.63)	0.484
Hemiplegia	2 (1.57)	3 (0.68)	0.342
Falls	10 (7.87)	63 (14.29)	0.057
Alcoholism	5 (3.94)	34 (7.71)	0.138
Risk Factors (≤91d)			
Recent hospitalization (≥3d)	69 (54.33)	191 (43.31)	0.028
Ongoing pregnancy	1 (0.79)	29 (6.58)	0.979
Recent delivery	1 (0.79)	18 (4.08)	0.246
Major surgery	24 (18.90)	43 (9.75)	0.005
Anemia	49 (38.58)	81 (18.37)	0.0001
Thrombocytopenia	8 (6.30)	6 (1.36)	0.002
Recent major bleeding (within 1 year)	24 (18.90)	56 (12.70)	0.077
Initial VTE presentation			0.22
Pulmonary embolism	48 (37.80)	300 (68.03)	
Deep vein thrombosis	79 (62.20)	141 (31.97)	

Table 2.2. Odds ratios of bleeding in patients with cancer stratified by cancer site along with the mean age and gender distribution

Site of Cancer	n (%)	Odds ratio (95% CI)	p-value	Mean Age	Sex (females)
Colorectal cancer	15 (3.09)	1.13 (0.61-2.09)	0.69	65.67 ± 2.66	4 (26.67)
Cancer of the small intestine	1 (4.76)	2.97 (0.37-23.79)	0.30	57 ± 0.0	0 (0)
Hepatobiliary and pancreatic cancer	10 (4.69)	1.46 (0.67-3.18)	0.35	62.1 ± 3.58	5 (50)
Gastric cancer	7 (7.78)	2.60 (1.09-6.19)	0.03	73.29 ± 4.58	4 (57.14)
Lung cancer	8 (1.27)	0.66 (0.30-1.45)	0.30	61 ± 3.79	2 (25)
Cancer of the kidney, bladder and prostate	21 (3.48)	1.46 (0.90-2.39)	0.13	75 ± 2.75	2 (9.52)
Breast cancer in women	4 (0.99)	0.64 (0.23-1.77)	0.39	63.5 ± 9.75	4 (100)
Endometrial cancer	3 (3.06)	1.25 (0.37-4.18)	0.72	69.67 ± 5.78	3 (100)
Metastases	36 (2.1)	2.87 (0.54-15.18)	0.21	62.94 ± 2.48	14 (38.89)

Table 2.3. Incidence rates if bleeding in cancer compared to non-cancer associated VTE according to the bleeding site.

	Cancer-associated VTE	**Non-cancer associated VTE**	
Site of bleeding	**n (%)**	**n (%)**	**p-value**
GI* bleed	116 (91.34)	407 (92.29)	0.046
GU* bleed	0 (0.00)	3 (0.68)	0.811
IC* bleed	3 (2.36)	19 (4.31)	0.000
Airways bleeding	8 (6.30)	12 (2.72)	0.063

GI: gastrointestinal – GU: genitourinary – IC: intracranial

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CHAPTER 3

DISCUSSION AND CONCLUSION

Cancer and cancer-related chemotherapy are considered a well-known cause of VTE, contributing to four-folds increase in the risk of VTE[1-3]. In turn, VTE is one of the leading causes of mortality in cancer patients and is associated with high morbidity risk in this population.[4, 5] The standard of care for cancer-associated VTE has been established by the CHEST guidelines in 2016.[6] LMWH is the first line therapy and is preferred over both the vitamin K antagonists (VKA) and the direct oral anticoagulants (DOAC). However, there is no difference in the use of the latter two options if LMWH cannot be used.[6] Anticoagulation should also be considered for an extended period of time in cancer patients, at least 6 months and this entails a higher frequency of associated complications such as VTE recurrence despite anticoagulation and bleeding while anticoagulated.[6, 7]

While the current practice nowadays consist of DOAC use for non-cancer associated VTE, most of the data available about the efficacy and safety of DOAC in treating VTE with cancer derive from subgroup analysis of cancer patients included in the clinical trials of VTE. Most recently in December 2017, the first randomized controlled trial comparing edoxaban to dalteparin in cancer patients was published.[8] It concluded that edoxaban was not inferior to dalteparin for the primary outcome but had a higher risk of bleeding compared to dalteparin (6.9% versus 4.0%, HR1.77). In this trial, gastrointestinal bleeding was the most common site of bleeding and mainly arose in patients with gastrointestinal cancer. These results keep the doors wide open on the applicability of other DOACs in the treatment of cancer-associated VTE, which remains the ultimate goal of VTE therapy in this specific population. For this reason, other trials are still ongoing comparing

rivaroxaban to dalteparin and apixaban to dalteparin with a targeted completion date of March 2018 and November 2018 respectively.[9, 10]

The most important clinical trials comparing treatment modalities and their bleeding outcomes in cancer patients with VTE will be discussed here. The CANTHANOX trial showed that the major bleeding rates (16%) was higher in the warfarin compared to the enoxaparin group (7%).[11] The CLOT[12], ONCENOX[13] and LITE[14] trials did not find any significant difference between LMWH and oral VKA in terms of major bleeding. The bleeding rates were 6 and 4% respectively in the dalteparin and coumadin groups of the CLOT trial (p=0.27).[12]

The CATCH trial[15] is a large study to assess how effective and safe is the use of tinzaparin compared to warfarin in the treatment of VTE in patients with active cancer. The rates of major bleeding were similar between the two arms of the sudy (2.7 vs 2.4%, p=0.77).

3.1. **SUMMARY OF RESULTS**

The main objective of this study is to highlight one of the most serious complications of VTE and its impact on a particularly vulnerable population. Thus, we aimed at studying the bleeding risk in cancer patients with VTE in Alberta, Canada over a decade and study the risk differnce between cancer sites.

3.1.1. Incidence of bleeding in VTE

Bleeding occurred in 1.79% of all patients with first time VTE. The incidence of bleeding was higher in the cancer-associated group (2.46%) than the non-cancer associated (1.66%) ($p<0.001$) which is in line with previous studies.[7, 16-18]. Our bleeding rates were lower than most of the rates previously studied but was very similar to the CATCH trial where beeding occurred in 2.7% and 2.4% of cancer patients treated with tinzaparin and warfarin respectively.[15] In

contrast, most of the clinical trials described bleeding frequency ranging between 4 and 10% in the general population.[12-14, 19] Considering the cancer population itself, the rates of bleeding were inconsistent among studies and they ranged as low as 1% by the RIETE investigators[17] and as high as 17.7% by Khorana et al.[20] The disparity in numbers likely reflects the heterogeneity of cancer patients with a wide variety of populations being studied.

3.1.2. Effect of cancer site on the risk of bleeding

Little is known about the influence of cancer site on the risk of bleeding and it is still not very clear if VTE-associated complications vary with the cancer site.[21] We found that gastrointestinal cancers were associated with a higher risk of bleeding followed by genitourinary cancer. There were few discrepancies between studies on the most common cancer site deemed responsible of higher risk of bleeding but most agreed on the prevalence of genitourinary and gastrointestinal cancers as potential contributors to bleeding in VTE.[7, 21] In our study, lung and breast cancers were not associated with a higher risk of bleeding. Monreal et al[17] also noted the absence of fatal bleeding in breast cancer patients. On the contrary, Mahe et al noted that lung cancer accounted for 1.8 times higher risk of bleeding.[21] This could be related probably to the type of tumour and the degree of invasion of the vasculature or to the degree of associated thrombocytopenia. It could also be influenced by the type of chemotherapy used or the type of anticoagulation used.

We did not find a significant difference in mean age between cancer site groups that could potentially explain higher risk of bleeding in some sites compared to others.

3.1.3. Bleeding site

There was no significant difference in the site of bleeding between cancer-associated and non-cancer associated VTE. Gastrointestinal bleeding was by far the most frequent site of bleeding. Airway and intracranial bleeding were present as well in about 6 and 3% of cancer patients. However, genitourinary bleeding were missing in our study. Common sites of bleeding reported in the recent literature include gastrointestinal, genitourinary and intracranial bleeding.[19, 21]

3.2. STRENGTHS OF THE STUDY

The AB-VTE database used in this study is a true representation of the population in Alberta. It was created by linking five provincial administrative health databases in Alberta based on fiscal year from April 2002 to March 2012 and which includes: the ambulatory care database involving both the emergency department and the outpatient clinic visits, the hospital inpatient discharge database, the physician claims database, the population registry and the vital statistics that gives information on death in Alberta. Additionally, the case definition of VTE was validated against chart audits in Alberta and had a high positive predictive value of 83.1%.[22] Briefly, our data is representative of Alberta and can be generalizable to the entire province as it involves all residents of Alberta, 18 years of age and older having encountered a first episode of VTE.

3.3. LIMITATIONS OF THE STUDY

The retrospective nature of our cohort study superimposes some limitations. First, the definition of bleeding does not totally match that of the ISTH criteria.[23] The International Society on Thrombosis and Haemostasis (ISTH) defined major bleeding in non-surgical patients as the presence of fatal bleeding and/or a symptomatic bleeding in a critical organ and/or a drop in

hemoglobin level of at least 2g/dl or resulting in a need for transfusing at least 2 units of red or whole blood cells. In our case, we defined bleeding based on the presence of diagnostic bleeding codes of the most common bleeding sites (intracranial, gastrointestinal, genitourinary, airways and intra-articular) because it is not feasible to determine whether it is symptomatic or not and unfortunately we did not have access to laboratory data. Second, the data is missing important laboratory information. Therefore, the definition of anemia or thrombocytopenia was also mainly based on diagnostic codes rather than laboratory values. Same issue applies to INR and other coagulation tests. Third, our information on cancer is limited. We do not know the TNM classification, histology, grade. We do not know if the cancer is active, whether it is has been treated or currently on treatment and what type of chemotherapy is used. That being said, we are not able to identify how sick the patients are or if their cancer is aggressive. However, we did have information about the presence of metastases. Finally and unfortunately, we were lacking information on anticoagulation use, choice, duration and course.

3.4. STUDY SIGNIFICANCE

Our study provides important information about the risk of bleeding in a vulnerable population that is often excluded from clinical trials for many reasons, namely ethical purposes and severity of clinical situation. It reinforces that bleeding risk is higher in cancer patients and that cancer site determines the risk of bleeding. Therefore, it permits to consider targeting the management strategies to each type of cancer and to implement strategies to mitigate bleeding and improve patients outcomes.

We are aware of the some questions were left unanswered with regards to whether the patients who bled were on any type of anticoagulation and whether they had active cancer, treated or not and the chemotherapy regimen used if any. We would like to expand our data in the future and

append the medication data (Pharmaceutical Information Network, PIN) and the laboratory data (Data Integration, Measurement and Reporting, DIMR) and also to include the most recent era where the use of direct oral anticoagulants has become popular.

3.5. CONCLUSION

Venous thromboembolism is associated with high morbidity and mortality. Despite advancements in medical therapy, data on VTE complications are still limited and they all depict that cancer patients developing VTE are at significantly higher risk of complications compared to the rest of population. In addition to that, we found the risk of bleeding differs by cancer site. We think that this area of VTE complications in the cancer population is underinvestigated and further studies are needed to find the most effective and safest approach to treat VTE in each cancer type.

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