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靜脈血栓栓塞症於癌症病人之流行病學與治療現況

Epidemiology and Clinical Profile of Venous Thromboembolism in Cancer Patients

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本論文係周丹薇君（R99451011）在國立臺灣大學臨床藥學研究所完成之碩士學位論文，於民國 101 年 07 月 05 日承下列考試委員審查通過及口試及格，特此證明。

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中文摘要

研究背景　靜脈血栓栓塞症(venous thromboembolism)對癌症病人的死亡率和疾病狀況的顯著影響，已是重要的臨床的問題。以往的研究顯示，不同種族的靜脈血栓栓塞症發生率不同。雖然在西方國家對靜脈血栓栓塞症的預防已有完整的治療指引可遵循，但是在亞洲國家，有關靜脈血栓栓塞症的流行病學資料卻仍然有限。

研究目的　本群體觀察性研究(population-based observational study)的目的乃為建立臺灣癌症病人發生靜脈血栓栓塞症的流行病學資料，分析發生靜脈血栓栓塞症的危險因子，並探討其臨床特徵和目前國內的治療現況。

研究方法　本研究以臺灣健保資料庫 2000 年、2005 年和 2010 年三套百萬人承保抽樣歸人檔為資料來源，找出 2001 年至 2008 年住院主診斷為癌症的新診斷癌症病人，並以初次住院主診斷為癌症的入院日期為 index date。在 index date 的住院主診斷有兩個(含)以上的癌症的病人，則被排除在研究之外。本研究的研究終點為 index date 當天或之後因靜脈血栓栓塞症而住院。本研究共有兩個靜脈血栓栓塞症的定義：定義一為住院檔中出現靜脈血栓栓塞症的診斷，定義二則為住院檔中同時有靜脈血栓栓塞症診斷及靜脈血栓栓塞症的治療。本研究針對所有癌症病人和不同癌症部位的靜脈血栓栓塞症的發生率，及針對發生靜脈血栓栓塞症和沒有發生靜脈血栓栓塞症的病人在年齡、性別、共病症和可能危險因子，連續變項使用 t-test，類別分項使用 Chi-square 或 Fisher's exact test 進行分析。針對以定義二而住院的病人，則使用邏輯迴歸模型(logistic regression model)進行分析，找出發生靜脈血栓栓塞症的危險因子，並探討靜脈血栓栓塞症長期治療的狀況、復發率與發生出血性副作用的機率。

研究結果　在 43,855 名新診斷癌症病人中，1388 名(3.2%) (定義一)和 473 名(1.1%) (定義二)病人在 index date 當天或之後因靜脈血栓栓塞症而入院。靜脈血栓栓塞症的發生率分別為 9.9 每 1,000 人年(1.0 – 68.2 每 1,000 人年) (定義一)和 3.4 每 1,000 人年(0.0 – 16.1 每 1,000 人年) (定義二)。靜脈血栓栓塞症發生率較高的癌症包括：

肝臟、胰臟、肺臟、多發性骨髓瘤(multiple myeloma)、肉瘤(sarcoma)和非何杰金氏淋巴瘤(non-Hodgkin's lymphoma)。靜脈血栓栓塞症(定義一)在 index date 30 天、90 天、180 天和 365 天內的累積發生率(cumulative occurrence)分別為 42.9%、53.5%、61.7%和 70.8%。靜脈血栓栓塞症(定義二)在 index date 30 天、90 天、180 天和 365 天內的累積發生率分別為 25.2%、39.8%、47.8%和 59.4%。靜脈血栓栓塞症的顯著危險因子包括癌症部位、之前有發生靜脈血栓栓塞症的病史、動脈栓塞症(arterial embolism)、肥胖(obesity)、高血壓、風濕性疾病、接受化學治療、合併治療和胸腔、腹部或泌尿生殖道大手術。三個月內的輸血治療與靜脈血栓栓塞症風險的降低有關。在 1,388 位因靜脈血栓栓塞症(定義一)住院的病人中，只有 33.6%的病人(n=467)在當次住院中有接受抗凝血劑的治療或接受栓塞切除術。在 473 位因靜脈血栓栓塞症(定義二)住院的病人中，1.5%的病人(n=7)接受栓塞切除術，其他病人則接受肝素(heparin)或低分子量肝素(low molecular weight heparin)作為靜脈血栓栓塞症的初期治療。81 個病人(19.5%)在第一次靜脈血栓栓塞症後有復發現象。在 415 個存活病人中，266 個病人(64.1%)有接受靜脈血栓栓塞症的長期治療，其中 72.2%的病人(n=192)接受 warfarin 作為長期治療靜脈血栓栓塞症的藥物。長期治療的時間長度中位數為 66 天，其中大約三分之二(58.7%, n=156)的病人的治療時間長度小於或等於 3 個月。

結論 雖然臺灣的癌症相關靜脈血栓栓塞症的發生率比高加索族群的發生率來的低，但其發生率比一般亞洲族群(general population)要高得多，尤其是在特定的癌症如：多發性骨髓瘤、胰臟癌、肝癌和肺癌。大部分的靜脈血栓栓塞症發生在癌症新診斷後一年內。在臺灣，目前的治療現狀與國外的臨床治療指引並不一致。靜脈血栓栓塞症的治療和預防可能需要更加完善，特別是針對發生靜脈血栓栓塞症危險性較高的病人。

關鍵詞 靜脈血栓栓塞症、癌症、流行病學、治療現狀、危險因子、全民健康保險研究資料庫

Abstract

Background Venous thromboembolism (VTE) is an increasing clinical problem in cancer patients that results in significant mortality and morbidity. Reports indicated that the incidence of VTE varies among different ethnic populations. Although the clinical guidelines for the prevention of VTE have been suggested in Western countries, the understanding of the epidemiology of VTE in Asian countries remains limited.

Objectives The goal of this population-based observational study is to explore the epidemiology of VTE among cancer patients in Taiwan, analyze the risk factors for VTE and describe the clinical characteristics and treatment pattern of VTE

Methods Using three sets of longitudinal health insurance database (LHID 2000, LHID 2005 and LHID 2010), we identified newly diagnosed cancer patients who have been hospitalized with a primary diagnosis of malignant disease between 2001 and 2008. The date when the patient was first hospitalized with a primary diagnosis of malignant disease was defined as the index date. Patients had more than one primary diagnosis of malignant diseases at index date were excluded. Primary endpoint of our study was hospital admission for VTE during or after index date. Two definitions of VTE were adopted in our study. VTE definition 1 was based on VTE diagnosis codes in the inpatient medical claims. VTE definition 2 was based on both the VTE diagnosis codes and management of VTE. The incidence rates of VTE for the entire study cohort and

subgroups of patients categorized by sites of cancer were estimated. Differences in age, gender, comorbidities, and potential risk factors for VTE between patients with and without VTE events were analyzed. We use t-test for continuous variables and Chi-square analysis or Fisher's exact test for discrete variables. Only patients who hospitalized with VTE (definition 2) were included in the logistic regression model to identify the risk factors for VTE. We also describe the long-term treatment pattern of VTE and incidence rates of recurrent VTE and bleeding complications.

Results Among 43,855 newly diagnosed cancer patients, 1388 (3.2%) (definition 1) and 473 (1.1%) (definition 2) patients were hospitalized for VTE during or after index date. The incidence rates of VTE (definition 1 and definition 2) were 9.9 per 1,000 person-years (1.0-68.2 per 1,000 person-years) and 3.4 per 1,000 person-years (0.0-16.1 per 1,000 person-years), respectively. The incidence rates were higher in certain cancers, particularly cancer of liver, pancreas, lung, multiple myeloma, sarcoma, and non-Hodgkin's lymphoma. The cumulative occurrence of VTE (definition 1) within 30, 90, 180, and 365 days after index date were 42.9%, 53.5%, 61.7%, and 70.8%, respectively. Cumulative occurrence of VTE (definition 2) within 30, 90, 180, and 365 days after index date were 25.2%, 39.8%, 47.8% and 59.4%, respectively. Significant risk factors for VTE were site of cancer, prior history of VTE, arterial embolism, obesity, hypertension, rheumatologic diseases, chemotherapy, combination therapy and major

thoracic, abdominal or urogenital surgery. In contrast, blood transfusion within 3 months was significant associated with reduced risk of VTE. Among 1388 patients who hospitalized with VTE (definition 1), only 33.6% of patients (n=467) received anticoagulant therapy or thromboectomy during the hospitalization. Among 473 patients who hospitalized with VTE (definition 2), 1.5% of patients received thromboectomy, other patients received heparin or low molecular weight heparin for initial treatment of VTE. Eighty-one patients (19.5%) had recurrent VTE after the first VTE event. Of 415 survived patients, long-term anticoagulant therapy was initiated in 266 patients (64.1%), 72.2% of them (n=192) received warfarin alone. The median duration was 66 days. Approximately two-thirds of patients (58.7%, n=156) received ≤ 3 months of long-term anticoagulant therapy.

Conclusions Although the incidence of cancer-related VTE among Taiwanese is lower than Caucasians populations, it is much higher than Asian general populations, particularly in patients with certain cancers such as multiple myeloma, pancreas, liver, and lung cancer. Most VTE occurred within 1 year after cancer diagnosis. Adherence to treatment guidelines was poor in Taiwan. Treatment and prophylaxis of VTE should be optimized, especially in patients with higher-risk of VTE.

Keywords Venous thromboembolism, cancer, epidemiology, clinical profile, risk factors, National Health Insurance Research Database

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Chapter 1 Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is an increasing clinical problem in cancer patients that results in significant mortality and morbidity. Cancer patients have 4- to 7- folds higher risk for VTE than general population, occurring in 4% to 20% of patients.[1,2] Use of anticoagulants, increased risk of VTE recurrence, bleeding complications during anticoagulant therapy, post-thrombotic syndrome and reduced lung function due to chronic thrombotic pulmonary hypertension further complicate the clinical management of cancer and worsen patients' quality of life.[3,4] Besides, cancer patients who develop VTE have a significant worse survival and this effect is more pronounced in patients with loco-regional disease rather than distant metastatic disease.[5-7]

Solid tumors of gastrointestinal (GI) tract, lungs, pancreas, ovaries, and hematological malignancies are associated with high risk of VTE, with the highest risk occurring during the initial period after cancer diagnosis.[5,9-11] Other risk factors for VTE among cancer patients including older age, metastatic stage, prior history of VTE, presence of indwelling central venous catheter (CVC), chemotherapy or hormone therapy, major surgery, inherited or acquired thrombophilia, and elevated pre-chemotherapy platelet count.[1]

The incidence of VTE in Asian population has been perceived to be lower than Caucasian population. However, the incidence of VTE in Asian population increased rapidly by 56% from 2004 to 2008.[8] Increased awareness of physicians, easier diagnosis of VTE, growing elderly population, and a Westernized lifestyle may contribute to this increasing trend.[9] While several nationwide epidemiologic studies had been performed using Taiwan's and Korea's National Health Insurance (NHI) database to understand the incidence and risk factors for VTE among the general population, only few in cancer patients. [8,10,11]

In addition, existing studies among Asian populations only focused on patients with colorectal, gastric, and pancreatic cancers, diffuse large B cell lymphoma, and multiple myeloma.[12-18] Furthermore, very few Small numbers of patients were included in these studies. Most existing studies only included patients from one medical center.[12-18] Up to know, the clinical significance of VTE among cancer patients, and the epidemiological study of VTE across various cancer subtypes have never been conducted in Asian populations. Given the growing incidence of cancer and elderly population, burden of VTE is expected to be increased. An epidemiological study will help us to understand the incidence and treatment of VTE among cancer patients and optimize the clinical practice. Therefore, a population-based study was performed using the Taiwan's NHI database to understand the epidemiology and clinical profile of VTE in cancer patients.

Chapter 2 Literature Review

2.1 Venous Thromboembolism

2.1.1 Overview of Venous Thromboembolism

VTE refers to all forms of pathologic thrombosis occurring within the venous circulation, represents a spectrum from simple superficial thrombophlebitis to fatal pulmonary embolism. Most venous thrombosis occurs at the deep veins of the lower extremities, giving rise to deep vein thrombosis (DVT). They also can occur in other parts of body, including the veins of the upper extremities, pelvis, abdomen, and cerebral venous sinuses. Pulmonary embolism (PE) is the most life-threatening manifestation of VTE, which occurs when a clot dislodges from the site of formation and embolizes into pulmonary arteries. Death from PE can occur within minutes after the onset of symptoms, before effective treatment is given.[19,20]

2.1.2 Epidemiology of Venous Thromboembolism

The actual incidence of VTE is unknown because the disease is often clinically silent. The annual incidence rate of VTE is reported to be 104-183 events per 100,000 persons in the Caucasian populations (Table 2.1).[21-25] The annual incidence of VTE increases markedly with age, from less than 5 cases per 100,000 persons under 15 year-old to 149 events per 100,000 persons over the age of 80.[21]

The prevalence of VTE varies among different ethnic cohorts. Compared to Caucasian populations, the incidence of VTE is significantly higher among African-American and significantly lower among Asian populations.[22,26,27] Among Asian populations, the estimated annual incidence of VTE is 14-57 per 100,000 persons (Table 2.1).[8,10,28,29] The incidence ranges from 2.5 events per 100,000 person-years in those younger than 30 years to 100 events per 100,000 person-years in those aged over 80 years.[10] Although the annual incidence of VTE among Asian populations has been perceived to be lower than Caucasian populations, it appears to be rapidly increasing.[8,30] Along with rapid aging of the population, VTE is a major healthcare problem which causing significant mortality, morbidity and healthcare resource expenditure in our aging society.

Table 2.1 Incidence of venous thromboembolism reported in different populations

		Incidence per 100,000		
Location	**Study design**	**VTE**	**DVT**	**PE**
America				
Minnesota (Silverstein et al. 1998)[21]	Population-based study	117	48	69
California (only Caucasian)[22] (White et al. 2005)	Population-based study	104		
Worcester (Spencer et al. 2009)[31]	Population-based study	114	95	34
Europe				
French (Oger et al. 2000)[24]	Population-based study	183	124	60
Norway (Naess et al. 2007)[25]	Cohort-study	143	93	50
Asia				
Hong Kong (Cheuk et al. 2004)[28]	Population-based study	21	17	3.9
Singapore (Molina et al. 2009)[29]	Population-based study	57		
Taiwan (Lee et al. 2010)[10]	Population-based study	15.9		
Korea (Jang et al. 2011)[8]	Population-based study	13.8	5.31	7.01

2.1.3 Risk Factors for Venous Thromboembolism

VTE is a multifactorial condition involving genetic and both constant and transient acquired risk factors. In 1884, Virchow's triad first described three primary factors contribute to the formation of thrombosis: abnormalities in blood flow (venous stasis), abnormalities in blood constituents (hypercoagulability), and abnormalities in the vessel wall (vascular endothelial injury). Risk factors for VTE, include increasing age, malignancy, prolonged immobility, major surgery, major trauma, prior VTE, chronic heart failure, and inherited or acquired thrombophilia, alter one or more of the components of the triad (Table 2.2).[32] There is convincing evidence that the risk of VTE increases in proportion to the number of predisposing factors.[32,33]

Compared with residents in the community, hospitalization without surgery or nursing home confinement is associated with 8-folds increased risk of VTE.[34] Hospitalization and nursing home residence together account for almost 60% of incident VTE events occurring in the community, with hospitalization for medical illness and hospitalization for surgery accounted for 22% and 24% of VTE, respectively.[2]

Table 2.2 Risk factors for venous thromboembolism

Strong risk factors (odd ratio > 10)
Fracture (hip or leg)
Hip or knee replacement
Major general surgery
Major trauma
Spinal cord injury
Moderate risk factors (odd ratio 2-9)
Arthroscopic knee surgery
Central venous lines
Chemotherapy
Congestive heart or respiratory failure
Hormone replacement therapy
Malignancy
Oral contraceptive therapy
Paralytic stroke
Pregnancy (postpartum)
Previous venous thromboembolism
Thrombophilia
Weak risk factors (odd ratio < 2)
Bed rest > 3 days
Immobility due to sitting (e.g. prolonged car or air travel)
Increasing age
Laparoscopic surgery (e.g. cholecystectomy)
Obesity
Pregnancy (antepartum)
Varicose veins

Adapted from Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. Circulation 2003;107:I9-16.

2.1.4 Complications of Venous Thromboembolism

VTE is an important worldwide healthcare burden associated with significant morbidity and mortality. It is reported to be the third common cardiovascular causes of death after myocardial infarction and stroke.[35] The 1-week survival rate after a PE is only 71%, and almost 25% of all cases of PE essentially present as sudden death.[36] In USA, 100,000-300,000 VTE-related deaths occur every year and PE had been declared to be the most common preventable cause of hospital death and the significant target to improve patient safety in hospitals.[37]

Recurrence of VTE is common. Despite anticoagulant therapy, about 30% of patients develop recurrent VTE within the next ten years, with the highest recurrence rate within the first year after their first VTE event.[38,39] Men have a higher rate of recurrence than women (relative risk of recurrent VTE: 1.6).[40,41] In addition, survivors of VTE always suffer from long-term complications, including post-thrombotic syndrome and chronic thrombotic pulmonary hypertension. One-third to one-half of patients with lower extremity DVT develop post-thrombotic syndrome during 20 years of follow-up, characterized by pain and swelling, and in severe cases with venous ulceration. These conditions can be disabling for patients and have great impact on healthcare costs. Subsets of VTE patients require long-term anticoagulation to prevent additional clots, which also decreases their quality of life and places them at an

increased risk for adverse bleeding episodes.[37,38]

2.1.5 Clinical Presentations of Venous Thromboembolism

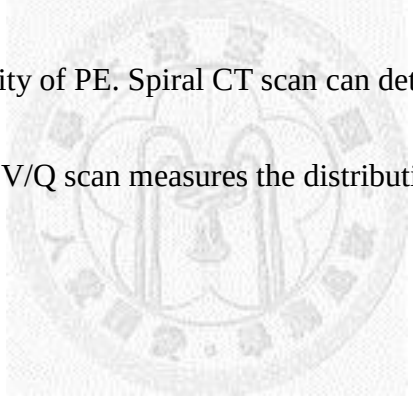
The signs and symptoms of VTE are nonspecific. Furthermore, many patients with VTE were asymptomatic. A leg DVT commonly presents with pain, erythema, and swelling of the affected limb. Physical examination may show palpable cord, warmth, and unilateral edema.[42,43] Patients with upper extremity or neck DVT often complain with upper extremity or head or neck swelling, erythema, and/or discomfort.[44] Symptoms associated with PE depend on the degree of vascular obstruction, the magnitude of inflammatory response, and the patient's cardio-pulmonary reserve. Patients may present with dyspnea, hypoxemia, tachycardia, pleuritic chest pain, hemoptysis or even collapse with shock or pulseless electrical activity cardiac arrest.[20,43]

2.1.6 Diagnosis of Venous Thromboembolism

Duplex ultrasonography remains the test of choice in the investigation and diagnosis of clinically suspected DVT. Although ultrasound is highly sensitive for the detection of proximal DVT, it is less accurate for isolated DVT of the calf. The ideal method, invasive venography, is used when a definitive answer is required. Newer image modalities such as magnetic resonance venography and computerized

tomography (CT) scan can detect thrombosis of vessels proximal to the inguinal ligament and intra-abdominal vessels. Another advantage of magnetic resonance venography and CT scan is their ability to provide information about surrounding structures that may lead to alternative diagnosis.[20,42-44]

Gold standard for the diagnosis of PE is pulmonary angiography, but it is an invasive procedure that involves injection of contrast dye into pulmonary artery and associated with 0.5% of mortality. Nowadays, CT scan has become the most commonly used imaging test to diagnose PE. Before CT scan, ventilation-perfusion (V/Q) scan was the first-line imaging modality of PE. Spiral CT scan can detect emboli in the pulmonary arteries whereas V/Q scan measures the distribution of blood and air flow in the lungs.[20,42,43]



2.2 Venous Thromboembolism in Patients with Cancer

2.2.1 Overview

VTE is a major complication of cancer and is one of the leading causes of death in patients with cancer.[1,4,45] The risk of VTE is higher in cancer patients than the general population, especially hospitalized patients with cancer and those receiving active therapy. In a population-based study, malignancy alone was associated with a 4-folds increased risk of VTE, whereas the use of chemotherapy increased the risk to 6.5-folds.[34] Overall, approximately 20% to 39% of VTE cases were attributable to active malignant disease.[33,46]

2.2.2 Epidemiology of Cancer-related VTE

The reported incidences of VTE in cancer patients have varied widely, with reported incidences ranging from 0.6% to 12.1% (Table 2.3 and 2.4).[47-54] However, the reported rates of VTE in cancer patients are believed to be underestimated, given that autopsy rates of VTE can be as high as 50% compared with clinical rates of 4% to 20%.[1] In addition, the burden of VTE in cancer patients is increasing. In previous study, the rate of VTE event in cancer patients increased by 28% over the period 1995–2003 ($p < 0.0001$ for the trend).[51]

The risk of postoperative VTE in cancer patients also exceeds that of non-cancer

surgical patients by 2- to 3-folds. Without anticoagulant prophylaxis, the incidence of postoperative DVT ranges from 40% to 80%.[55] In an observation study using administrative database, the rate of VTE in cancer patients within 30 days post-admission after major surgery was 3.5%, with ranging by procedure from 1.8 to 13.2%.[56] Another prospective study, focused on postoperative clinical overt VTE, reported an incidence of 2.1% even when in-hospital prophylaxis was given in 81.6% of the patients. The 30-day mortality was 1.7% and VTE was adjudicated as the most common of death (19 of 41 cases, 46.3%) in the study.[57]

2.2.3 The Pathogenesis of VTE in Cancer

Cancer cell may induce thrombosis by triggering several complex prothrombotic pathways, including procoagulant effects of tissue factors expressed by tumor cells, the release of cytokines, the inhibition of fibrinolysis, and the overexpression of membrane adhesion molecules. Furthermore, solid tumor-mediated extrinsic vascular compression and invasion can obstruct venous return, resulting in blood flow stasis, endothelial cell injury, and coagulation activation. Malignancy-associated inflammation can also result in increased concentrations of acute-phase proteins such as factor VIII, fibrinogen, and von Willebrand factor. Elevations of these acute-phase proteins are associated with an increased risk of thrombosis.[3,58]

Table 2.3 Cohort studies of incidence of venous thromboembolism in patients hospitalized with cancer

Location	Data source	Study population	Study endpoint	No. of patients	VTE event (%)
USA Levitan et al. (1999)[47]	Medicare database	Patients ≥ 65 years with malignant disease	Hospital admission for DVT and/or PE	1,211,944	0.6 (0.16-1.20)
USA Sallah et al. (2002)[48]	Medical records of University of Tennessee Health Science Center, University of North Carolina at Chapel Hill, and East Carolina University	Patients with solid tumor	Objectively confirmed DVT and/or PE	1,041	7.8
USA Stein et al. (2006)[49]	National Hospital Discharge Survey	Patients with malignant disease	Hospital admission for DVT and/or PE	40,787,000	2.0 (0.60-4.30)
USA Khorana et al. (2006)[50]	Discharge database of the University Healthsystem Consortium	Adult cancer patients with febrile neutropenia	Hospital admission for VTE	5,272	5.4 (2.74-12.10)
USA Khorana et al. (2007)[51]	Discharge database of the University Healthsystem Consortium	Adult patients with solid tumor	Hospital admission for VTE	1,015,598	4.1 (1.90-8.10)
Denmark Cronin-Fenton et al. (2010)[52]	Database of Danish National Registry of Patients, Danish Cancer Registry and Danish Civil Registration System	Patients ≥ 15 years with malignant disease	Hospital admission for VTE	57,591	1.8 (0.80-4.00)

Table 2.4 Cohort studies of incidence of venous thromboembolism in ambulatory cancer patients receiving active therapy

Location	Data source	Study population	Study endpoint	No. of patients	VTE event (%)
USA Khorana et al. (2005)[53]	Database of Awareness of Neutropenia in Cancer Study Group Registry	Patients ≥ 18 years with histologically confirmed diagnosis of cancer	VTE	3,003	1.93
USA Shah et al. (2010)[54]	Clinical trial research database of Merorial Sloan Kettering Cancer Center	Patients ≥ 18 years with non-hematologic malignancies	Objectively confirmed DVT/PE	2,120	5.45

2.2.4 Risk Factors for Cancer-related VTE

Despite the overall increased risk of VTE among cancer patients, VTE risk is especially high among certain subgroups, such as hospitalized patients, those receiving active neoplastic therapy or hormone therapy, those undergoing major surgery, and those with metastatic disease. The risk of VTE differs across various cancer subgroups and over the natural history of cancer. Sites of cancer with highest rates of VTE include pancreas, stomach, brain, ovary, kidneys, lungs, and hematologic malignancies, such as multiple myeloma and non-Hodgkin's lymphoma. The risk of VTE is highest in the initial period after the cancer diagnosis.[1,4,5,51]

Cancer patients receiving active therapy are at greater risk of VTE. In a retrospective cohort study of 1,015,598 cancer patients, use of chemotherapy is identified to be an independent risk factor for VTE.[51] Recent study among chemotherapy-treated patients with lung cancer found that use of chemotherapy is associated with 30% greater risk of VTE compared with patients not receiving chemotherapy.[59] Hormone therapy (such as tamoxifen) and antiangiogenic drug (such as bevacizumab) have been associated with an increased risk of VTE.[1,60,61] Among patients with multiple myeloma, the risk of VTE is higher in whom receiving thalidomide or lenalidomide in combination with dexamethasone or chemotherapy. Besides, erythropoietin-stimulating agents (ESA) are also associated with an increased risk of

VTE.[1]

Other risk factors for VTE among cancer patients include increasing age, prior history of VTE, pre-chemotherapy platelet count ≥ 350,000 μL, the presence of prothrombotic mutation, placement of CVC, and concomitant comorbid conditions. Race is also a significant factor associated with VTE risk. Compared with Caucasian patients with cancer, Asian patients with cancer have significant reduced risk of VTE.[6,7,51] A comprehensive list of risk factors associated with VTE in cancer patients is summarized in Table 2.5.[1]

Table 2.5 Risk factors for venous thromboembolism in patients with malignant disease

Patient-related factors
Older age
Race (higher in African Americans; lower in Asian-Pacific Islanders)
Comorbid conditions (obesity, infection, renal disease, pulmonary disease, arterial thromboembolism)
Prior history of VTE
Elevated pre-chemotherapy platelet count
Heritable prothrombotic mutations
Cancer-related factors
Primary site of cancer (GI, brain, lung, gynecologic, renal, hematologic)
Initial 3-6 months after diagnosis
Current metastatic disease
Treatment-related factors
Recent major surgery
Current hospitalization
Active chemotherapy
Active hormonal therapy
Current or recent antiangiogenic therapy (thalidomide, lenalidomide, bevacizumab*)
Current erythropoiesis-stimulating agents
Presence of central venous catheters

* Bevacizumab is clearly associated with an increased risk of arterial thrombotic events; an association with venous thrombosis is not fully established.

Adapted from Lyman GH, Khorana AA, Falanga A, et al. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol 2007;25:5490-505.

2.2.5 Consequences of Cancer-related VTE

VTE is associated with significant morbidity and mortality among cancer patients. In a retrospective analysis based on California cancer registry, development of VTE after cancer diagnosis was a significant predictor of mortality within 1 year, with hazard ratios (HR) ranging from 1.6 to 4.2 ($p < 0.01$). The strongest predictor of death in that study was metastatic disease at the time of cancer diagnosis, with an HR ranging from 1.8 to 49.0 ($p<0.001$).[7] Similar finding was shown in another retrospective study included hospitalized neutropenic cancer patients. Patients with VTE had 2-folds greater risk of mortality than patients without diagnosis of VTE.[50] Studies in patients with colorectal, lung and breast cancer in California also found that VTE is a significant predictor of death within 1 year of cancer diagnosis. The effect was more pronounced in patients with loco-regional stage rather than patients with advanced and metastatic disease.[6,7,62] Similar finding was found in other studies in patients with pancreatic, gastroesophageal, bladder, and ovarian cancer.[54,63-65]

VTE is also associated with hospitalization, anticoagulants use, reduced pulmonary function, and post-thrombotic syndrome. The occurrence of VTE may interfere with planned chemotherapy and causes treatment delay.[4] Furthermore, compared with general population, the risk of recurrent VTE and bleeding complications during anticoagulant treatment in cancer patients was increased about 4 times and 2 times,

respectively.[66] The occurrence of VTE worsens patients' quality of life and lead to increased consumption of healthcare resource. In a retrospective study of medical records of 529 cancer patients using medical records as the data source, the mean hospitalization cost for DVT was $20,065 per episode (2002 US$) compared with a cost of $7712 to $10,804 per episode in a general medical population with VTE.[67]

2.2.6 Treatment of Venous Thromboembolism in Cancer Patients

In response to the increasing concern regarding VTE in cancer patients, several international cancer organizations have recently issued guidelines regarding its treatment and prevention. These include the Italian Association of Medical Oncology (AIOM),[68] the National Comprehensive Cancer Network (NCCN),[69] the American Society of Clinical Oncology (ASCO),[1] the European Society of Medical Oncology (ESMO),[70] and the French National Federation of the League of Centers Against Cancer (FNCLCC).[71,72] Anticoagulant therapy remains the cornerstone of VTE treatment. Anticoagulant therapy is divided into two phases: initial treatment to minimize the risk of thrombus extension and subsequent fatal PE, and long-term treatment to prevent recurrent VTE, thereby reducing the risk of post-phlebitic syndrome.[73]

2.2.6.1 Initial Treatment of Venous Thromboembolism

When VTE is objectively confirmed, parenteral anticoagulants should be initiated. Treatment is started with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux. Agent selection should be individualized according to characteristics of the individual agents (ease of administration, reversibility, half-life, and cost) and patient's clinical situation (inpatient or outpatient status, renal function, medical or surgical patient). In most circumstances, LMWH is preferred because it is recommended for the long-term treatment of VTE in patients with cancer and facilitates the transition to outpatient management. [1,44,69-71] Furthermore, LMWH and fondaparinux provide additional advantages over UFH, including better bioavailability after subcutaneous administration, longer half-life, more predictable anticoagulant response and lower incidence of heparin-induced thrombocytopenia.[74] LMWH should be used cautiously in patients with creatinine clearance (CCr) < 30 mL/min and fondaparinux is contraindicated in these patients.[1,69,70]

2.2.6.2 Long-term Treatment of Venous Thromboembolism

After initial treatment for 5 to 10 days, LMWH is the preferable approach for long-term treatment lasting at least 3 to 6 months for patients with VTE. Vitamin K antagonists (VKA) with a target international normalized ratio (INR) of 2 to 3 are

considerable choice for long-term treatment when LMWH is not available or in patients with severe renal insufficiency. Indefinite therapy may be required for patients with active cancer, such as those with metastatic disease and those receiving chemotherapy or hormonal therapy. [1,69,70,75] Although enoxaparin and tinzaparin also have been studied in open-label randomized controlled trials in cancer patients, the efficacy of dalteparin is supported by the highest quality evidence and it is the only LMWH approved by the FDA for long-term treatment of VTE in cancer patients.[69] Randomized controlled trials indicate that LMWH is more effective than VKA in long-term treatment for preventing VTE recurrence with similar bleeding risk.[76-79] The CLOT (Randomized Comparison of LMWH versus Oral Anticoagulant for The Prevention of Recurrent VTE in Patients with Cancer) study demonstrated a relative risk reduction of 49% with LMWH versus a VKA.[77] In patients with contraindications to anticoagulation, inferior vena cava filter is an alternative but anticoagulant therapy should be resumed once the bleeding risk is resolved. Dosage regimens and recommendations for treatment of VTE in patients with cancer are provided in Table 2.6 and 2.7.[1,69,70,75]

On the other hand, cancer patients are more likely to have thrombosis in uncommon sites such as the veins of upper extremities, vena cava, visceral, portal, or cerebral circulation.[80] There are no specific guidelines and randomized controlled trials focus on the treatment of abdominal DVT in cancer patients or non-cancer patients.

Recently, the 9th American College of Chest Physicians (ACCP) guidelines published in 2012 recommend anticoagulation over no anticoagulation in patients with symptomatic splanchnic vein thrombosis.[75]

Treatment of VTE in cancer patients is more challenging than general population. Compared with those without malignancy, VTE recurs 3-folds more frequently in cancer patients and they are more prone to bleeding complications during long-term treatment of VKA therapy despite a stable INR between 2 to 3. Interactions between VKA and chemotherapeutic agents may cause elevation of INR and clinically relevant bleeding. Tendencies toward thrombocytopenia, osteopenia, malnutrition, brain metastasis and hepatic metastasis all further complicate thrombosis care in cancer patients.[3,55]

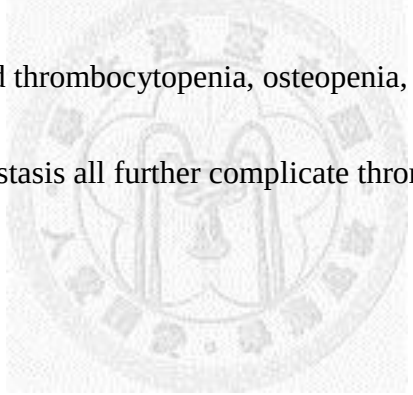


Table 2.6 Regimens for prophylaxis/treatment of VTE in patients with cancer

Management	Drug	Regimen
Prophylaxis		
Hospitalized medical or surgical cancer patients	Unfractioned heparin	5,000 U every 8 hours
	Dalteparin	5,000 U daily
	Enoxaparin	40 mg daily
	Fondaparinux	2.5 mg daily
Treatment of established VTE		
Initial	Heparin	80 U/kg IV bolus, then 18 U/kg/h IV
	Dalteparin	100 U/kg every 12 hours 200 U/kg daily
	Enoxaparin	1 mg/kg every 12 hours 1.5 mg/kg daily
	Tinzaparin	175 U/kg daily
	Fondaparinux	< 50 kg, 5.0 mg daily 50-100 kg, 7.5 mg daily > 100 kg, 10.0 mg daily
Long term	Dalteparin	200 U/kg daily for 1 month; then 150 U/kg daily
	Warfarin	5-10 mg PO daily; adjust dose to INR 2-3

Adapted from Lyman GH, Khorana AA, Falanga A, et al. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol 2007;25:5490-505.

Table 2.7 Recommendations for treatment of VTE in cancer patients

	ASCO[1]	**NCCN**[69]	**ESMO**[70]	**ACCP**[75]
Initial treatment of VTE	LMWH is the preferred approach for the initial 5-10 days	LMWH, UFH or fondaparinux according to patient's characteristics and clinical situation	Weight-adjusted dose LMWH. If Ccr < 25-30 mL/min, either UFH or LMWH with anti-Xa monitoring	Suggest LMWH or fondaparinux over UFH for minimum of 5 days
Long-term treatment of VTE	LMWH for at least 6 months is preferred; VKA are acceptable when LMWH is not available. Indefinite anticoagulation in patients with active cancer	LMWH is preferred; 3-6 months for DVT and 6-12 months for PE. Indefinite anticoagulation in patients with active cancer or persistent risk factors	LMWH is preferred for 6 months with 75-80% of the initial dose. Long-term LMWH for patients with active cancer	Suggest extended anticoagulant therapy (~3 months to indefinite); LMWH is preferred over VKA therapy
Thrombolytic therapy in the initial treatment	Restricted to patients with life- or limb-threatening thrombotic events	Patients with massive PE or submassive PE with moderate or severe RV enlargement or dysfunction	Restricted to patients with PE presenting with severe RV dysfunction, or limb-threatening thrombotic events	Restricted to patients with massive PE and impending venous gangrene
Inferior vena cava filters	Restricted to patients with contraindications to anticoagulation or recurrent VTE despite adequate long-term LMWH	Contraindications to failure of anticoagulation; cardiac or pulmonary dysfunction severe enough to make any new PE life-threatening or multiple PE with chronic pulmonary hypertension	Contraindications to anticoagulation or recurrent PE despite adequate long- term LMWH. Resume anticoagulation on the risk of bleeding is reduced	Contraindications to anticoagulation or recurrent PE despite adequate long-term LMWH. Start anticoagulation if the risk of bleeding is resolved

Table 2.7 Recommendations for treatment of VTE in cancer patients (continued)

	ASCO[1]	**NCCN**[69]	**ESMO**[70]	**ACCP**[75]
Treatment of catheter-related thrombosis	NA	Anticoagulation for as long as catheter is in place and for at least 3 months after catheter removal	NA	3 months of anticoagulation if the catheter is removed; continue anticoagulation as long as the CVC remains

Abbreviations: VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; ESMO, European Society of Medical Oncology; UFH, unfractionated heparin; LMWH, low molecular weight heparin; VKA, vitamin K antagonist; RV, right ventricular; Ccr, creatinine clearance; NA, not addressed.

2.2.7 Prevention of Venous Thromboembolism in Cancer Patients

2.2.7.1 Prevention of VTE in Cancer Patients Undergoing Surgery

Cancer patients who undergo surgery are at high risk of developing VTE. Post-operative VTE occurs 2- to 3-folds more frequent in cancer patients compared with non-cancer patients. Prophylaxis of VTE with low-dose UFH, LMWH or fondaparinux is recommended in all patients undergoing major surgery (such as laparotomy, laparoscopy, or thoracotomy lasting > 30 minutes). Pharmacological prophylaxis should be started as soon as possible and continued for at least 7 to 10 days postoperatively unless contraindicated. Extended prophylaxis up to 4 weeks may be considered in patients undergoing major abdominal or pelvic surgery for cancer patients with high-risk features such as residual malignant disease after operation, obese patients, and those with a previous history of VTE. [1,69,70]

LMWH has shown to be as effective and safe as low dose UFH in preventing post-operative VTE.[81-83] In a double-blind randomized trial of fondaparinux versus dalteparin in high-risk abdominal surgery patients, postoperative fondaparinux was at least as effective as perioperative dalteparin.[84] However, after pooling the results of studies in patients undergoing elective hip replacement, elective knee replacement, and hip fracture surgery, it is suggested that compared to LMWH, fondaparinux does not reduce clinically significant VTE events but leads to more major bleeding events.[75]

Mechanical prophylaxis such as pneumatic calf compression (IPC) may be added to pharmacological prophylaxis but should not be used as monotherapy for VTE prevention unless pharmacological prophylaxis is contraindicated because of active bleeding.[1,70] Mechanical prophylaxis alone can reduce the rate of DVT by 66% but achieve only a non-statistical 33% risk reduction in the rate of PE.[55] Combination of mechanical and pharmacological prophylaxis may improve efficacy in the very high risk patients.[1] Dosage regimens and recommendations for prevention of VTE in patients with cancer are provided in Table 2.6 and 2.8.[1,69,70]

2.2.7.2 Prevention of Hospitalized and Ambulatory Cancer Patients

Hospitalized cancer patients should be considered to receive anticoagulation for prevention of VTE.[1,69,70] Among patients hospitalized for cancer, chronic heart disease, severe infectious diseases, or lung disease, cancer patients had the highest incidence of VTE (7.6%) compared to the average rate of all patients being 5.6%.[85] Previous randomized clinical trials have demonstrated that pharmacological prophylaxis leads to a lower VTE incidence compared with placebo, without increasing major bleeding.[86-88]

Routine prophylaxis with anticoagulants is not recommended in ambulatory patients with cancer except patients with multiple myeloma receiving thalidomide or lenalidomide with chemotherapy or dexamethasone. ESMO guideline recommended

LMWH, aspirin, or adjusted-dose warfarin (INR ~1.5) while ASCO guideline recommended LWMH or adjusted-dose warfarin (INR ~1.5). Prophylaxis in cancer patients receiving chemotherapy and/or hormone therapy is not recommended.[1,70] For cancer patients with indwelling CVC, benefit of pharmacological prophylaxis had not been shown. Current guidelines do not support the use of anticoagulants for VTE prophylaxis.[70,72]

Table 2.8 Recommendations for prophylaxis of VTE in cancer patients

	ASCO[1]	NCCN[69]	ESMO[70]
Hospitalized cancer patient	• Prophylactic anticoagulation should be considered in the absence of bleeding or other contraindications to anticoagulation		
Surgical cancer patient	• All patients undergoing major surgical* intervention for malignant disease should be considered for thromboprophylaxis, commenced preoperatively, or as early as possible postoperatively and continue for 7 to 10 days. • Extended prophylaxis up to 4 weeks in patients undergoing major abdominal or pelvic surgery for cancer with high-risk features such as residual disease, obesity, or prior VTE	• Pharmacologic thromboprophylaxis should be used in the absence of contraindications • Prophylaxis should be continue for the duration of hospitalization • Extended prophylaxis up to 4 weeks after surgery for high-risk abdominal or pelvic surgery, defined by gastrointestinal malignancy, prior VTE, anesthesia time > 2 hours, bed rest > 4 days, advanced stage, age > 60 years	• Thromboprophylaxis should be considered in all patients undergoing major cancer surgery* • Prophylaxis should be continued for at least 10 days postoperatively • Extended prophylaxis up to 1 month after surgery in cancer patients undergoing elective major abdominal or pelvic surgery
Ambulatory patient	• Not recommended with the exception of LMWH, aspirin or adjusted- dose warfarin (INR ~1.5) in patients with multiple myeloma receiving thalidomide- or lenalidomide-based combination regimens		
Patients with CVC	• NA	• Prophylactic anticoagulation is not recommended	• Prophylactic anticoagulation is not recommended

***** Laparotomy, laparoscopy, or thoracotomy lasting > 30 minutes

Abbreviations: VTE, venous thromboembolism; ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; ESMO, European Society of Medical Oncology; LMWH, low molecular weight heparin; NA, not addressed.

2.2.8 Venous Thromboembolism in Asian Patients with Cancer

Previous cohort studies had demonstrated that Asian patients with cancer have significant reduced risk of VTE compared with Caucasian patients with cancer.[6,7,51] However, population-based epidemiological studies in Asian demonstrated a yearly increased incidence of VTE in Asians.[8] Recently, several studies focused on VTE among cancer patients in Asian populations had been published. Incidence of VTE in multiple myeloma, gastric cancer, colorectal cancer, advanced pancreatic cancer, diffuse large B-cell lymphoma, and cholangiocarcinoma ranged from 3.7% to 10.6% (Table 2.9).[12-18]

VTE incidence among patients with multiple myeloma receiving thalidomide- or lenalidomide- based combination therapy was 5.3%, which is lower than that reported in Western countries (10 to 20%).[13] In a retrospective study among patients with colorectal cancer based on database of Seoul National University Bundang Hospital found that the 2-year cumulative incidence of VTE was 3.6%. The 2-year cumulative incidence of DVT/PE ranged from 0.3%, 0.9%, 1.4% and 6.4% in stages 0-1, 2, 3, and 4, respectively.[15] Development of DVT/PE but not intra-abdominal venous thrombosis was related to increased mortality in both patients with loco-regional and metastatic disease. Similar finding was shown in another study in patients with gastric cancer.[14] Although Asian patients with loco-regional malignant disease had lower VTE incidence than

Western populations, the VTE incidence is similar among patients with distant malignant disease. The incidence of VTE among Japanese patients with DLBCL was reported to be comparable with that in Caucasian populations.[16] On the other hand, the risk of postoperative VTE was much lower than in Caucasian patients (~0.2%) but further investigations are needed to confirm this finding.[14,15]

Table 2.9 Cohort studies of incidence of venous thromboembolism in patients of specified cancer site among Asian population

Location	Data source	Study population	Study endpoint	No. of patients	VTE event (%)
Korea Oh et al. (2008)[12]	Electronic medical records database of Seoul National University Bundang Hospital	Patients with advanced pancreatic cancer	Objectively confirmed VTE	132	5.3
Korea Koh et al. (2010)[13]	Korean multiple myeloma registry	Patients received thalidomide for multiple myeloma	Objectively confirmed symptomatic VTE	360	3.9
Korea Lee et al. (2010)[14]	Electronic medical records database of Seoul National University Bundang Hospital	Patients with gastric cancer	Objectively confirmed extremity venous thrombosis, PE and intra-abdominal thrombosis	2,085	3.8*
Korea Choi et al. (2011)[15]	Electronic medical records database of Seoul National University Bundang Hospital	Patients with colorectal cancer	Objectively confirmed extremity venous thrombosis, PE and intra-abdominal thrombosis	2,006	3.6*
Japan Yokoyama et al. (2011)[16]	Medical records database of Keio University Hospital	Patients with diffuse large B-cell lymphoma	Objectively confirmed symptomatic VTE	142	10.6
Korea Kang et al. (2012)[17]	Medical records database of Asan Medical Center, Seoul	Patients with advanced gastric cancer	Objectively confirmed DVT/PE	3,095	4.9*
Korea Jeon et al. (2012)[18]	Medical records database of Pusan National University Hospital	Patients with cholangiocarcinoma	Objectively confirmed VTE (including intra-abdominal thrombosis)	273	3.7

* 2-year cumulative incidence

Chapter 3 Study Objective

Using the administrative claims data from the NHI database, the goal of this population-based cohort study were:

(1) to explore the incidence date and timing of VTE,

(2) to identify the risk factors for VTE,

(3) to describe the clinical characteristics and treatment pattern of VTE,

(4) to examine the incidence of recurrent VTE and bleeding complications during long-term treatment of VTE among cancer patients.

Chapter 4 Materials and Methods

4.1 Data Source

This population-based cohort study was based on Longitudinal Health Insurance Database (LHID) of National Health Insurance research database (NHIRD) in Taiwan. The NHI program was organized by the government and operated by Taiwan's Bureau of the NHI. This mandatory, single-payer health insurance was launched in 1995, and has covered over 99% of Taiwan's population (approximately 23 million residents) and contracted with 97% of hospital as well as clinics throughout the nation. It provides comprehensive benefits, including inpatient care, ambulatory care, dental care, and prescription drug coverage, to all beneficiaries. Registration datasets and claims databases of all beneficiaries in the NHI program have been maintained since 1997 and offer an excellent opportunity to conduct studies.[89,90]

This study uses LHID 2000, LHID 2005 and LHID 2010 as data source. LHID 2000, LHID 2005 and LHID 2010 contain all the original claim data of 1,000,000 beneficiaries randomly sampled from the year 2000, 2005, and 2010 Registry for Beneficiaries (ID), respectively. All traceable personal identifiers are removed from the database to protect patient confidentiality.[90] The databases used in this study included all inpatient and outpatient medical claims from January 1, 1999 to December 31, 2009.

4.2 Study Population and Study Outcomes

4.2.1 Study Cohort

Our study population included newly diagnosed cancer patients who have been hospitalized with a primary diagnosis of malignant disease, identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code (ICD-9-CM codes: 140.x-208.xx) between January 1, 2001 and December 31, 2008. Diagnoses in NHI research databases are coded using the ICD-9-CM coding scheme since 2000.[89] This time frame allowed for retrieving at least 1 year of baseline data prior to cancer diagnosis and up to 1 year of follow up after cancer diagnosis.

Major categories of malignant diseases that were included and their ICD-9-CM diagnosis codes were shown in Table 4.1. We used the year 1999 as a run-in year to identify incident cases of malignant diseases. The date when the patient was first hospitalized with a primary diagnosis of malignant disease was defined as the index date. Patients were excluded from this study if their genders were unknown or they had more than one primary diagnosis of malignant diseases at index date, for their cancer sites cannot be categorized.

Table 4.1 ICD-9-CM codes of inclusion diagnosis

Cancer site	ICD-9-CM codes
Head & neck cancer	140.x-149.x, 160.x-161.x
Esophageal caner	150.x
Stomach cancer	151.x
Colorectal cancer	153.x-154.x
Liver cancer	155.x
Pancreas cancer	157.x
Other abdominal cancers	152.x, 156.x, 158.x, 159.x
Lung cancer	162.x-163.x
Sarcoma	170.x-171.x
Skin cancer	172.x-173.xx
Breast cancer	174.x-175.x
Endometrial cancer and cervical cancer	179-182.x
Ovarian cancer	183.x
Prostate cancer	185
Testicular cancer	186.x
Bladder cancer	188.x
Renal cancer	189.x
Brain cancer	191.x-192.x
Thyroid cancer	193
Non-Hodgkin’s lymphoma	200.xx, 202.xx
Hodgkin’s lymphoma	201.xx
Multiple myeloma	203.xx
Leukemia	204.xx-208.xx

4.2.2 Primary Endpoint – Hospital Admission for VTE

Primary endpoint of our study was hospital admission for VTE, including venous thrombosis and pulmonary embolism, during or after index date. Two definitions of VTE were adopted in our study. VTE definition 1 was based on VTE diagnosis codes (ICD-9-CM codes in Table 4.2) in the inpatient medical claims. VTE definition 2 was based on both the VTE diagnosis codes and management of VTE (prescription of intravenous or subcutaneous (IV/SC) anticoagulants (UFH/LMWH) or reimbursement codes of surgical thromboectomy). Anatomic distribution of VTE and relevant ICD-9-CM codes were summarized in Table 4.3.

The date of the hospital admission for VTE was defined as the date of the VTE event. For those who did not have a VTE event, we first followed them until the end of the study period (December 31, 2009). However, in order to more precisely calculate their follow-up period, we check their medical utilization 1 year prior to December 31, 2009. We found that only 29,430 patients had inpatient or outpatient medical claim in the databases. Those patients without any medical claim might not survive until the period. Calculation of follow-up time until December 31, 2009 for all patients may underestimate the incidence rate of VTE. Therefore, the last outpatient or inpatient medical claim of each patient was extracted and the date of outpatient visit/hospital admission was defined as the end of follow-up date.

Table 4.2 ICD-9-CM diagnosis codes of venous thromboembolism

415.1: Pulmonary embolism and infarction

- 415.11: Iatrogenic pulmonary embolism and infarction
- 415.12: Septic pulmonary embolism
- 415.13: Saddle embolus of pulmonary artery
- 415.19: Other pulmonary embolism and infarction

451: Phlebitis and thrombophlebitis

- 451.0: Phlebitis and thrombophlebitis of superficial vessels of lower extremities
- 451.1: Phlebitis and thrombophlebitis of deep veins of lower extremities
  - 451.11: Phlebitis and thrombophlebitis of femoral vein (deep) (superficial)
  - 451.19: Phlebitis and thrombophlebitis of deep veins of lower extremities, other
- 451.2: Phlebitis and thrombophlebitis of lower extremities, unspecified
- 451.8: Phlebitis and thrombophlebitis of other sites
  - 451.81: Phlebitis and thrombophlebitis of iliac vein
  - 451.82: Phlebitis and thrombophlebitis of superficial veins of upper extremities
  - 451.83: Phlebitis and thrombophlebitis of deep veins of upper extremities
  - 451.84: Phlebitis and thrombophlebitis of upper extremities, unspecified
  - 451.89: Phlebitis and thrombophlebitis of other sites
- 451.9: Phlebitis and thrombophlebitis of unspecified site

452: Portal vein thrombosis

453: Other venous embolism and thrombosis

- 453.0: Budd-chiari syndrome
- 453.1: Thrombophlebitis migrans
- 453.2: Other venous embolism and thrombosis of inferior vena cava
- 453.3: Other venous embolism and thrombosis of renal vein
- 453.4:Acute venous embolism and thrombosis of deep vessels of lower extremity
  - 453.40 : Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity
  - 453.41: Acute venous embolism and thrombosis of deep vessels of proximal lower extremity
  - 453.42: Acute venous embolism and thrombosis of deep vessels of distal lower extremity

Table 4.2 ICD-9-CM diagnosis codes of venous thromboembolism (continued)

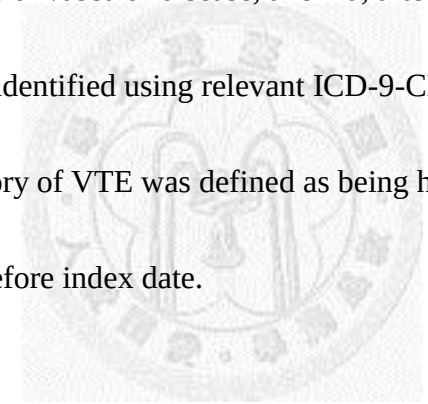
453.8: Acute venous embolism and thrombosis of other specified veins
453.81: Acute venous embolism and thrombosis of superficial veins of upper extremity
453.82: Acute venous embolism and thrombosis of deep veins of upper extremity
453.83: Acute venous embolism and thrombosis of upper extremity, unspecified
453.84: Acute venous embolism and thrombosis of axillary veins
453.85: Acute venous embolism and thrombosis of subclavian veins
453.86: Acute venous embolism and thrombosis of internal jugular veins
453.87: Acute venous embolism and thrombosis of other thoracic veins
453.89: Acute venous embolism and thrombosis of other specified veins
453.9: Other venous embolism and thrombosis of unspecified site

Table 4.3 Anatomic distribution of VTE and relevant ICD-9-CM codes

Location of VTE	**ICD-9-CM codes**
Pulmonary embolism	415.1x
Portal vein	452
Hepatic vein	453.0
Renal	453.3
Lower extremities	451.1x, 451.2, 451.81, 453.4x, 453.89
Upper extremities	451.83, 451.84, 451.89, 453.82-453.86
Vena cava	453.2, 453.87
Superficial veins	451.0, 451.82, 453.81
Unspecified or other	451.9, 453.1, 453.8, 453.9

4.2.3 Baseline Characteristics and Comorbid Diseases

Baseline characteristics retrieved from databases included age at index date and gender. For each patient the comorbid diseases were retrieved from both the outpatient and inpatient medical claims for 1 year before or during the index date. The comorbid diseases included hypertension, heart failure, ischemic heart disease, atrial fibrillation, renal insufficiency, liver disease, chronic lung disease, diabetes mellitus, stroke, rheumatologic diseases, varicose veins of lower extremities, degenerative and paralytic neurologic disease, peripheral vascular disease, anemia, arterial embolism and obesity. These comorbidities were identified using relevant ICD-9-CM diagnosis codes (Appendix 1). A prior history of VTE was defined as being hospitalized with VTE diagnosis within 2 years before index date.



4.2.4 Potential Risk Factors for VTE

Pregnancy, major surgery, hospitalization, major extremity trauma, major spine trauma, blood transfusion (including transfusion of blood and blood components), and infectious diseases were categorized as potential risk factors, and were recorded as present only if they were documented in inpatient or outpatient medical claims within 3 months before or during the VTE event or end of follow-up date. Hospitalization was defined as hospital admission ≥ 3 days within 3 months prior to VTE event or end of

follow-up date. The disease predisposing patients to VTE and procedures were identified using relevant ICD-9-CM diagnosis or procedure codes (Appendix 1). Operations were classified as major neurologic, thoracic, abdominal, urogenital, and orthopedic. Infectious diseases were classified as hospital-diagnosed infection if the diagnosis code was claimed from inpatient medical claims or outpatient-diagnosed infection if it was claimed from outpatient medical claims.

Active therapy of cancer was classified as: (a) chemotherapy (including biologic therapy), (b) radiation therapy, (c) hormone therapy, and (d) combination therapy. To assess the impact of active therapy on the development of VTE, patients were recorded as having received active therapy if records of active therapy were documented within 3 months before or during the VTE event or end of follow-up date. Chemotherapy, or biologic therapy was identified using ICD-9-CM codes for chemotherapy or biologic therapy (99.25, 00.15, 99.28, V58.1x, V67.2) and pharmacy dispensing fee for chemotherapeutic drugs (05211A), recorded as present if one of these present. Radiation therapy was identified using ICD-9-CM code (V58.0). A comprehensive list of potential risk factors and their relevant ICD-9-CM codes were summarized in Appendix 2. Use of hormone therapy (Table 4.4) was identified from prescriptions of both inpatient and outpatient medical claims. Combination therapy was defined as combined use of chemotherapy, radiation therapy or hormone therapy during the period. Association

between development of VTE and the use of granulocyte colony-stimulating factor (G-CSF), erythropoietin- stimulating agent (ESA), and thalidomide therapy were also assessed.

Table 4.4 List of hormone therapy

Classification	Medications
Aromatase Inhibitor	Aminoglutethimide
	Anastrozole
	Exemestane
	Letrozole
Antiestrogen	Tamoxifen
	Toremifene
LNRH analogs	Leuprolide
	Goserelin
	Triptorelin
Antiandrogens	Flutamide
	Bicalutamide
	Cyproterone

4.2.5 Treatment Pattern of VTE

We analyzed treatment patterns of both initial and long-term treatment for VTE among patients with a hospital admission for VTE. Initial treatment pattern of patients hospitalized with VTE (definition 1 or 2) was described. Initial treatment was defined as the treatment received during the first hospital admission for VTE and was categorized into thromboectomy, use of UFH, LMWH, and/or warfarin, and no anticoagulant therapy.

Patients hospitalized with VTE (definition 2) were followed to analyze the

long-term anticoagulant treatment pattern of VTE. The type and duration of anticoagulant treatment were recorded. Treatment duration was calculated from the discharge date of first hospitalization for VTE until the recurrence of VTE or end of follow-up date (Figure 4.2), based on the number of days supply documented in the prescriptions of the inpatient and outpatient medical claims. For outpatient medical claims, duration of anticoagulant therapy was based on the number of days supply in the prescriptions. For inpatient medical claims, duration of anticoagulant therapy was defined as the length of the hospital stay. Duration of long-term anticoagulant therapy was categorized into ≤ 3 months, 3-6 months, 6-12 months, and longer than 12 months.

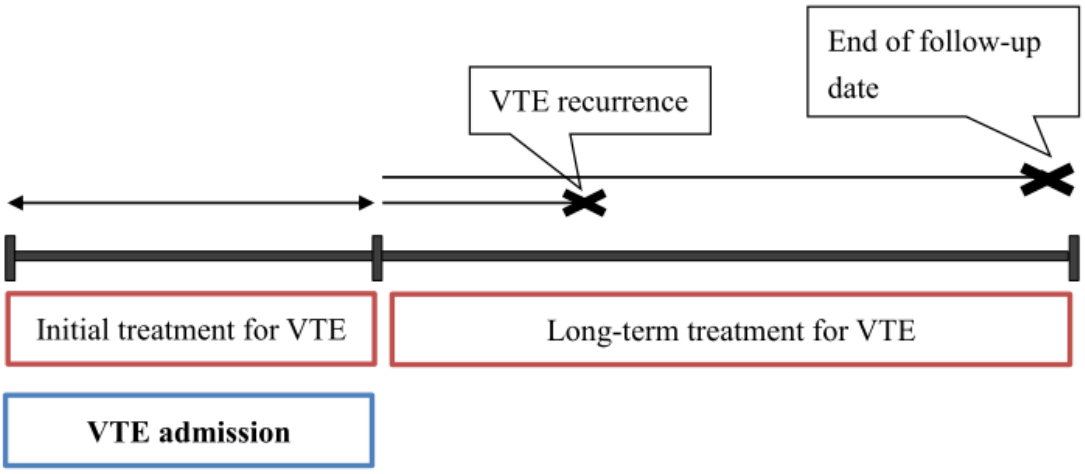


Figure 4.1 Initial and long-term treatment for VTE

4.2.6 Recurrence of VTE and Bleeding Complications

Cancer patients who hospitalized with VTE (definition 2) during or after index date were followed to analyze the incidence rates of VTE recurrence and bleeding complications. During the follow-up period, a recurrence of VTE was defined as a second hospitalization with a diagnosis of VTE and management of VTE (VTE definition 2) during the hospital stay after the first hospital admission for VTE. Bleeding complications were defined as a hospitalization with relevant ICD-9-CM codes indicating a cerebral or GI bleeding event (Table 4.5). All patients were followed from index date until the recurrence of VTE or end of follow-up date whichever comes first.

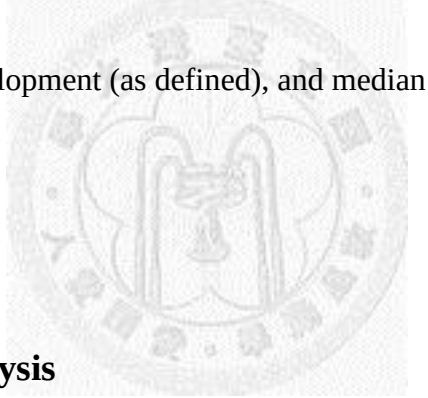
Table 4.5 Bleeding complications and relevant ICD-9-CM codes

Bleeding complications	**ICD-9-CM codes**
Cerebral	
Subarachnoid hemorrhage	430
Intracranial hemorrhage	431, 432.x
Gastrointestinal	
Gastric ulcer	531.xx
Duodenal ulcer	532.xx
Peptic ulcer	533.xx
Gastrojejunal ulcer	534.xx
Diverticulosis/diverticulitis of small intestine with hemorrhage	562.02, 562.03
Diverticulosis/diverticulitis of colon with haemorrhage	562.12, 562.13
Hemorrhage of the rectum or anus	569.3
Perforation of intestine	569.83
Angiodysplasia of intestine with haemorrhage	569.85
Dieulafoy lesion (hemorrhagic) of intestine	569.86
Gastrointestinal hemorrhage	578.x

4.3 Statistical Analysis

4.3.1 Incidence Rate of VTE

The incidence rates of VTE for the entire study cohort and subgroups of patients categorized by sites of cancer were estimated and expressed as the number of cases per 1,000 person-years. For VTE cases, person-years were calculated from index date to the date of VTE event. For patients without VTE event, person-years were calculated from index date until end of follow-up date. Among patients experiencing a VTE event, Time-to-VTE was defined as the time interval between index date and the first identified date of VTE development (as defined), and median time-to-VTE was reported.



4.3.2 Descriptive Analysis

Differences in age, gender, comorbidities, and potential risk factors for VTE between patients with and without VTE events were analyzed. Comparisons of continuous variables between these two groups were performed using Student's t-test and the data were described as means with standard deviations (SD). Comparisons of discrete variables were performed using the chi-square or Fisher's exact test and the data was presented as frequencies and percentages. Statistical significance was set at $p < 0.05$ and all tests were two-tailed.

4.3.3 Logistic Regression Analysis

To analyze the impact of age, gender, cancer site, comorbidities and potential risk factors associated with VTE development, logistic regression analysis reporting odds ratios (ORs) with 95% confidence intervals (CIs) was performed. Only patients who hospitalized with VTE (definition 2) were defined as having a VTE event in the logistic regression model. Malignant diseases with higher risk for VTE development, including GI tract (stomach, colorectum, pancreas, liver, and esophagus), brain, lung, endometrium and cervix, ovary, and kidney were grouped.[1] Hematological malignant diseases included non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, and leukemia. Other sites of cancer were grouped and used as reference to assess the risk for VTE associated with cancer site. Multivariate logistic regression models, using stepwise selection were carried out to identify the independent risk factors for development of VTE. The study framework of analysis of risks factors for development of VTE is shown in Figure 4.1. Statistical significance was set at $p < 0.05$.

4.3.4 Statistical Software

SAS software (Version 9.2; SAS Institute Inc., Cary, NC, USA) and Microsoft Office Excel 2010 were used in this study for the claims data conversion and analysis.

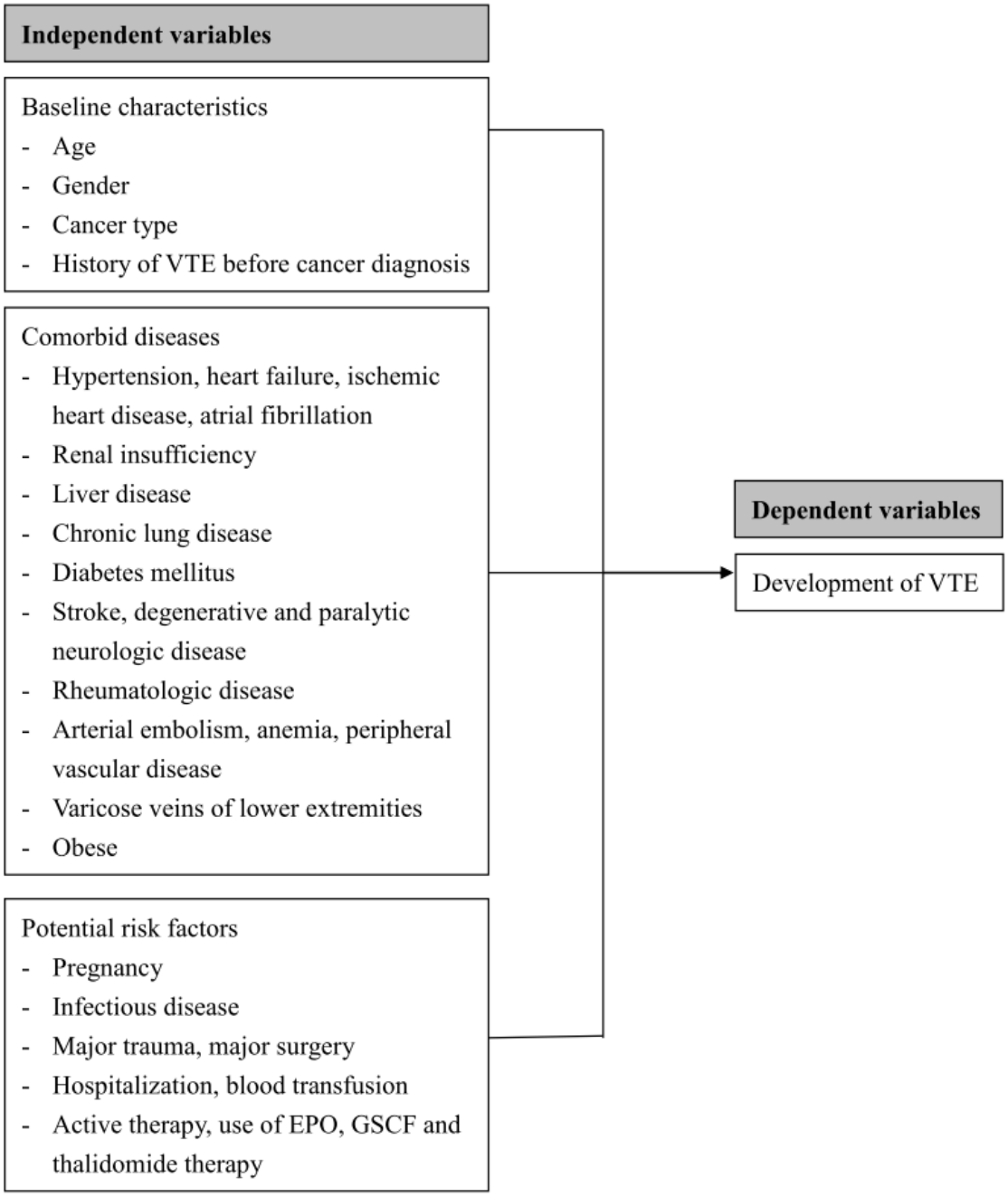


Figure 4.2 Study framework - risk factors for VTE development among cancer patients

Chapter 5 Results

5.1 Study Cohort

Between January 1, 2001 and December 31, 2008, 52,514 patients who had been newly hospitalized with a primary diagnosis of malignant disease were identified using ICD-9-CM codes from LHID databases. Seventeen patients whose gender cannot be identified were excluded. Another 15 patients were excluded because they had more than one primary diagnosis of malignant diseases at index date. In order to adopt a new cancer patient design, patients who hospitalized with any diagnosis of malignant disease (ICD-9-CM code 140.xx-208.xx) between January 1, 1999 and December 31, 2000 (n=7,104) were excluded. After excluding repeated subjects in LHID 2000, 2005 and 2010, 43,855 newly diagnosed cancer patients were included in our cohort study. The study flow-chart is shown in Figure 5.1.

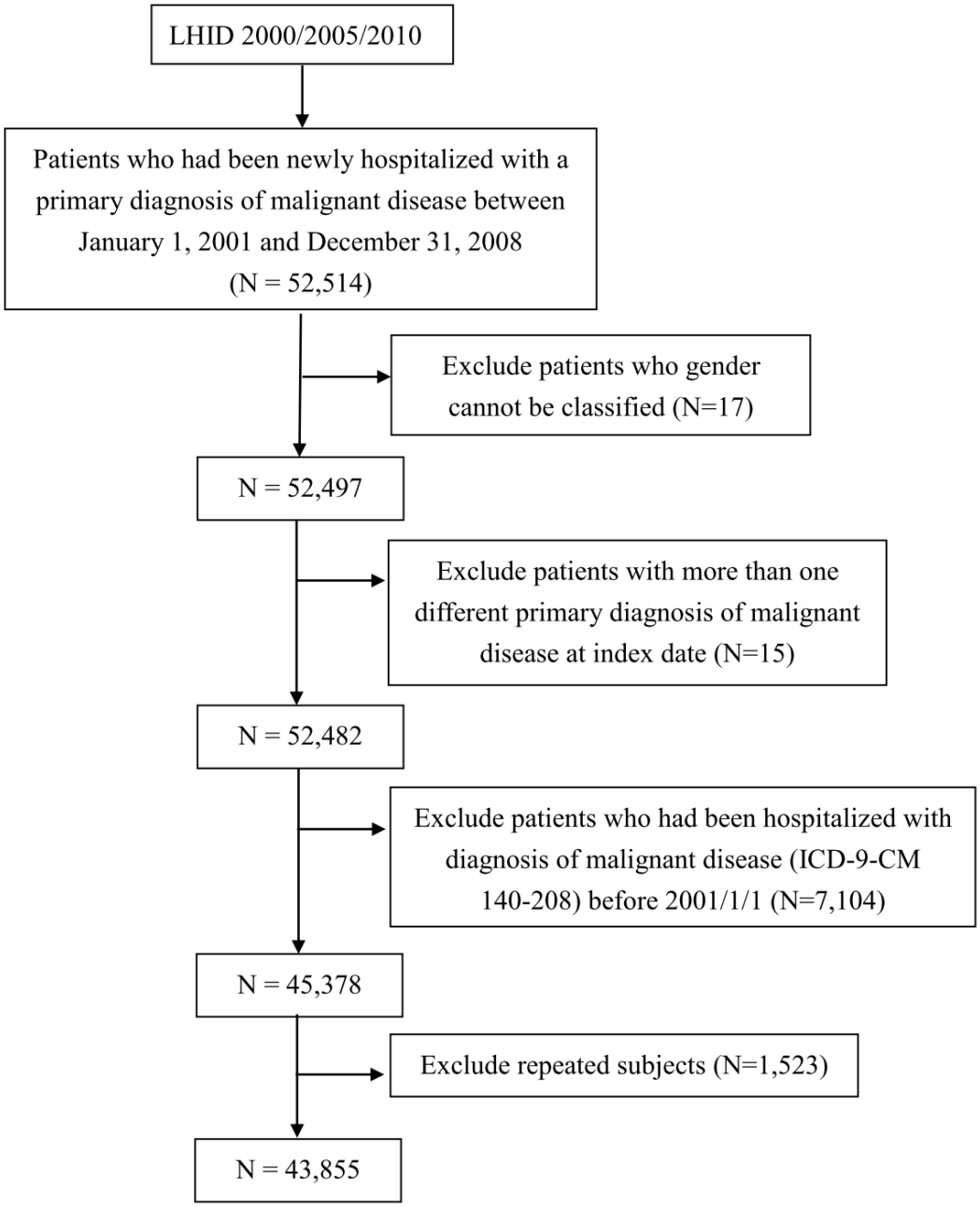


Figure 5.1 Flowchart of the population-based study

5.2 Patient Characteristics of Study Cohort

A total of 43,855 patients with first-ever hospitalization with a primary diagnosis of malignant disease between January 1, 2001 and December 31, 2008 were identified and comprised the study cohort. The mean age (± SD) of the study cohort was 59.5 years (± 15.9 years). Approximately half of them (52.7%) were men. Greater than one-thirds (41.9%) of patients were aged 65 years and older. Colorectal cancer (14.7%) was the most frequently diagnosed cancer in our study cohort, followed by breast cancer (13.8%), liver cancer (12.0%), head and neck cancer (10.0%), and lung cancer (9.5%), respectively. Together, these five cancers accounted for 60% of all newly diagnosed cancer patients in our cohort.

5.3 Incidence Rate and Clinical Characteristics of VTE

5.3.1 Incidence Rate of VTE

5.3.1.1 VTE (Definition 1)

Among 43,855 newly diagnosed cancer patients, hospital admissions for VTE (definition 1) were identified in 1,388 patients (3.2%) during or after index date. Among patients who hospitalized for a VTE event, 55.0% of them (n=764) had primary diagnosis of liver cancer. As shown in Table 5.1, the overall incidence rate of VTE (definition 1) was 9.88 per 1,000 person-years; the incidence rate was higher in men than women (13.56 versus 6.61 per 1,000 person-years).

The incidence rates of VTE were higher in certain cancers, particularly cancer of liver (68.23 per 1,000 person-years), pancreas (27.83 per 1,000 person-years), lung (17.22 per 1,000 person-years), multiple myeloma (10.56 per 1,000 person-years), and non-Hodgkin's lymphoma (9.32 per 1,000 person-years). Taken together, these five cancers accounted for 67.6% of the VTE cases (n=938). In contrast, the incidence rates of VTE were lower in thyroid cancer (1.00 per 1,000 person-years), breast cancer (1.77 per 1,000 person-years), head and neck cancer (2.68 per 1,000 person-years), Hodgkin's lymphoma (2.92 per 1,000 person-years), and skin cancer (3.21 per 1,000 person-years).

Table 5.1 Site of cancer and associated incidence rate of VTE (VTE definition 1)

	Total patient (n)	VTE cases (n)	Rate of VTE (%)	Observation time (p-y)[a]	Incidence of VTE (per 1,000 p-y)
All patients	43,855	1,388	3.2	140,524	9.88
Male	23,115	896	3.9	66,063	13.56
Female	20,740	492	2.4	74,461	6.61
Site of cancer					
Liver	5,272	764	14.5	11,197	68.23
Pancreas	618	19	3.1	683	27.83
Lung	4,159	121	2.9	7,025	17.22
Multiple myeloma	183	4	2.2	375	10.65
Non-Hodgkin's lymphoma	1,011	30	3.0	3,219	9.32
Leukemia	689	16	2.3	1,740	9.20
Renal	1,303	33	2.5	4,655	7.09
Sarcoma	458	12	2.6	1,761	6.82
Stomach	2,231	40	1.8	6,110	6.55
Ovary	668	15	2.3	2,390	6.28
Colorectum	6,462	112	1.7	22,452	4.99
Esophageal	761	6	0.8	1,239	4.84
Brain	522	7	1.3	1,559	4.49
Endometrium and cervix	2,327	43	1.9	10,024	4.29
Prostate	1,943	29	1.5	7,218	4.02
Bladder	1,723	23	1.3	6,477	3.55
Testis	119	2	1.7	582	3.44
Other abdominal	671	9	1.3	1,681	3.36
Skin	898	11	1.2	3,426	3.21
Hodgkin's lymphoma	85	1	1.2	342	2.92
Head and neck	4,390	40	0.9	14,922	2.68
Breast	6,035	45	0.8	25,438	1.77
Thyroid	1,327	6	0.5	6,009	1.00

Abbreviations: p-y, person-years

[a] For VTE cases, person-years were calculated from index date to the date of first hospitalization for VTE during or after cancer diagnosis. For patients without VTE event, person-years were calculated from index date until end of follow-up date.

5.3.1.2 VTE (Definition 2)

Hospital admissions for VTE (definition 2) were identified in 473 patients (1.1%) during or after index date. The incidence rates of VTE for the entire study cohort and subgroups of patients categorized by gender and sites of cancer are shown in Table 5.2. The overall incidence rate of VTE (definition 2) was 3.35 per 1,000 person-years, and the incidence rate was higher in men than women (3.89 versus 2.86 per 1,000 person-years). Among patients with VTE (definition 2), 22.2%, 15.2%, and 14.6% of them had primary diagnosis of liver, lung, and colorectal cancer, respectively.

The incidence rates of VTE were higher in certain cancers, particularly cancer of pancreas (16.05 per 1,000 person-years), lung (10.20 per 1,000 person-years), liver (9.06 per 1,000 person-years), multiple myeloma (7.92 per 1,000 person-years), and sarcoma (5.08 per 1,000 person-years). Taken together, these five cancers accounted for 42.3% of all VTE cases (n=200). In contrast, the incidence rates of VTE were lower in thyroid cancer (0.50 per 1,000 person-years), breast (0.50 per 1,000 person-years), and head and neck (1.34 per 1,000 person-years) cancer.

Table 5.2 Site of cancer and associated incidence rate of VTE (VTE definition 2)

	Total patient (n)	VTE cases (n)	Rate of VTE (%)	Observation time (p-y)[a]	Incidence of VTE (per 1,000 p-y)
All patients	43,855	473	1.1	141,304	3.35
Male	23,115	259	1.1	66,571	3.89
Female	20,740	214	1.0	74,734	2.86
Site of cancer					
Pancreas	618	11	1.8	685	16.05
Lung	183	72	1.7	7,058	10.20
Liver	5,272	105	2.0	11,593	9.06
Multiple myeloma	689	3	1.7	379	7.92
Sarcoma	4,159	9	2.0	1,773	5.08
Non-Hodgkin lymphoma	1,303	15	1.5	3,248	4.62
Ovary	1,011	11	1.7	2,405	4.57
Stomach	761	22	1.0	6,123	3.59
Renal	2,231	16	1.2	4,686	3.41
Esophageal	671	4	0.5	1,240	3.23
Brain	522	5	1.0	1,562	3.20
Endometrium and cervix	458	31	1.3	10,055	3.08
Colorectum	668	69	1.1	22,502	3.07
Prostate	6,462	20	1.0	7,232	2.77
Other abdominal	1,723	4	0.6	1,685	2.37
Leukemia	119	4	0.6	1,758	2.28
Bladder	2,327	14	0.8	6,484	2.16
Skin	1,943	6	0.7	3,436	1.75
Head and neck	4,390	20	0.5	14,955	1.34
Breast	898	29	0.5	25,485	1.14
Thyroid	85	3	0.2	6,020	0.50
Hodgkin's disease	6,035	0	0.00	348	0.00
Testis	1,327	0	0.00	590	0.00

Abbreviations: p-y, person-years.

[a] For VTE cases, person-years were calculated from index date to the date of first hospitalization for VTE during or after cancer diagnosis. For patients without VTE event, person-years were calculated from index date until end of follow-up date.

5.3.2 Clinical Characteristics of VTE Events

5.3.2.1 VTE (Definition 1)

Most VTE events (70.8%, n=981) occurred within 1 year after index date, with 35.8% of VTE events (n=497) occurred at index date (Table 5.3). Median time-to-VTE was 70 days (range, 0-3,124 days). Cumulative occurrence of VTE within 30, 90, 180, 270, and 365 days after index date were 42.9%, 53.5%, 61.8%, 66.3, and 70.8%, respectively.

Anatomic distribution of VTE is shown in Table 5.4.Among 1,388 patients with VTE events, 134 patients (9.7%) had PE events. Of them, 118 patients had PE alone, and 16 patients had concomitant PE and venous thrombosis (14 patients had concomitant PE and thrombosis of other unspecified site while 2 patients had concomitant PE and thrombosis of hepatic/portal vein).

Most patients had venous thrombosis (90.4%, n=1,254). Seven hundred and thirty-four patients (52.9%) had intra-abdominal venous thrombosis (thrombosis of renal, hepatic, or portal vein), 384 patients (27.7%) had thrombosis of other unspecified site. Only 73 (5.2%) and 38 (2.7%) patients had thrombosis of extremities and vena cava. Twenty-one patients (1.5%) had multiple thrombotic sites: 16 of them had concomitant thrombosis of vena cava and intra-abdominal venous, 1 patient had concomitant thrombosis of extremities and other unspecified site, and 3 patients had

concomitant thrombosis of vena cava, intra-abdominal venous and other unspecified site.

5.3.2.2 VTE (Definition 2)

Among patients hospitalized for VTE (definition 2), 59.4% (n=281) of VTE events occurred within 1 year after index date, and 18.0% of VTE events occurred at index date (Table 5.3). Median time-to-VTE was 222 days (range, 0-3,124 days). Cumulative occurrence of VTE within 30, 90, 180, 270, and 365 days after index date were 25.2%, 39.8%, 47.8%, 53.9, and 59.4%, respectively.

As shown in Table 5.4, 76 patients (16.1%) had PE and 15 patients (3.2%) had concomitant PE and venous thrombosis (14 patients had concomitant PE and thrombosis of other unspecified site and 1 patient had concomitant PE and thrombosis of hepatic vein). Three hundred and eighty-two patients (80.7%) had venous thrombosis. Ninety patients (19.0%) had intra-abdominal venous thrombosis and 255 patients (53.9%) had thrombosis of other unspecified site. Only 19 patients (4.0%) and 12 patients (2.5%) had thrombosis of extremities and vena cava. Six patients (1.3%) had multiple thrombotic sites: 4 patients had concomitant thrombosis of vena cava and intra-abdominal venous, and 2 patients had concomitant thrombosis of intra-abdominal venous and other unspecified site.

Table 5.3: Time-to-VTE after cancer diagnosis

	VTE definition 1 (N = 1,388)		VTE definition 2 (N = 473)	
Time-to-VTE	**Patient No. (%)**	**Cumulative rate of VTE (%)**	**Patient No. (%)**	**Cumulative rate of VTE (%)**
0 days	497 (35.8)	35.8	85 (18.0)	18.0
1 – 30 days	98 (7.1)	42.9	34 (7.2)	25.2
31 – 90 days	147 (10.6)	53.5	69 (14.6)	39.8
91 – 180 days	115 (8.3)	61.8	38 (8.0)	47.8
181 – 270 days	63 (4.5)	66.3	29 (6.1)	53.9
271 – 365 days	62 (4.5)	70.8	26 (5.5)	59.4
366 – 545 days	70 (5.0)	75.8	32 (6.8)	66.2
546 – 761 days	75 (5.4)	81.2	33 (7.0)	73.2
> 731 days*	261 (18.8)	100.0	127 (26.9)	100.0

* The last observed events occurred 3,124 days after index date

Table 5.4 Anatomic distribution of VTE

	VTE definition 1 (N = 1,388)	VTE definition 2 (N = 473)
Sites	**Patient No. (%)**	**Patient No. (%)**
Pulmonary embolism	118 (8.5)	76 (16.1)
Pulmonary embolism and venous thrombosis	16 (1.1)	15 (3.2)
Thrombosis of extremities	73 (5.3)	19 (4.0)
Thrombosis of vena cava	38 (2.7)	12 (2.5)
Thrombosis of renal vein, hepatic vein or portal vein	734 (52.9)[a]	90 (19.0)[b]
Thrombosis of unspecified site	384 (27.7)	255 (53.9)
Superficial venous thrombosis	4 (0.3)	0 (0.0)
Multiple thrombotic sites	21 (1.5)	6 (1.3)

[a] 715 patients had portal vein thrombosis, 12 patients had hepatic vein thrombosis, 7 patients had thrombosis of renal vein

[b] 86 patients had portal vein thrombosis, 2 patients had hepatic vein thrombosis, 2 patients had thrombosis of renal vein

5.4 Risk Factors for VTE

5.4.1 Baseline Characteristics, Comorbid Diseases and Potential Risk Factors

5.4.1.1 VTE (Definition 1)

As shown in Table 5.5, mean age (± SD) of cancer patients with VTE (definition 1) was 60.4 years (± 14.4 years), which were significantly older than cancer patients without VTE (59.5 ± 16.0 years). There were significantly more men (64.6% versus 52.3%, $p < 0.0001$) in patients with VTE events. Compared with cancer patients without VTE event, more cancer patients with VTE events had prior histories of VTE within 2 years before index date (1.0% versus 0.1%, $p < 0.0001$). Besides, there were significantly more patients had comorbid diseases of diabetes mellitus, liver disease, arterial embolism, and varicose veins of lower extremities among patients with VTE events than patients without VTE event.

Comparison of potential risk factors for development of VTE between patients with and without VTE events is shown in Table 5.6. There was no difference in the prevalence of pregnancy and major trauma. Compared with patients without VTE event, more patients with VTE received major surgery, active therapy, blood transfusion, and G-CSF, or diagnosed with infectious diseases within 3 months before/during the VTE event or end of follow-up date. Hospital admission was more frequent in patients with

VTE events (45.0% versus 31.2%, $p < 0.0001$). Among patients who received active therapy, more patients with VTE received chemotherapy (27.0% versus 11.8%, $p < 0.0001$), but more patients without VTE received hormone therapy (7.4% versus 2.7%, $p < 0.0001$).

Table 5.5: Baseline characteristics of the study population (VTE definition 1)

	Patients without VTE N = 42,467		**VTE (definition 1) N = 1,388**		**P-value**
Mean age (years)	59.51 ± 15.95		60.40 ± 14.38		0.0251*
	No.	**%**	**No.**	**%**	
Age groups (years)					<0.0001*
≤ 18	495	1.2	8	0.6	
19 – 40	4,355	10.3	112	8.1	
41 – 60	16,493	38.8	533	38.4	
61 – 80	17,759	41.8	651	46.9	
≥ 81	3,365	7.9	84	6.0	
Gender					<0.0001*
Male	22,219	52.3	896	64.6	
Female	20,248	47.7	492	35.4	
Prior history of VTE	58	0.1	14	1.0	<0.0001*
Hypertension	15,661	36.9	543	39.2	0.0884
Heart failure	1,759	4.1	65	4.7	0.3205
Ischemic heart disease	5,884	13.9	207	14.9	0.2620
Atrial fibrillation	633	1.5	19	1.4	0.7124
Renal insufficiency	3,201	7.5	122	8.8	0.0828
Chronic lung disease	8,030	18.9	276	19.9	0.3612
Diabetes mellitus	7,669	18.1	302	21.8	0.0004*
Stroke	2,642	6.2	78	5.6	0.3604
Degenerative & paralytic neurologic disease	3,602	8.5	110	7.9	0.4633
Rheumatologic diseases	559	1.3	26	1.9	0.0751
Liver disease	7,362	17.3	716	51.6	<0.0001*
Arterial embolism	161	0.4	11	0.8	0.0153*
Anemia	5,085	12.0	156	11.2	0.4063
Varicose veins of lower extremities	160	0.4	15	1.1	<0.0001*
Peripheral vascular disease	504	1.2	20	1.4	0.3912
Obesity	144	0.3	7	0.5	0.3430

* p-value < 0.05

Table 5.6 Potential risk factors for development of VTE (VTE definition 1)

	Patients without VTE N = 42,467		**VTE (definition 1) N = 1,388**		**P-value**
	No.	**%**	**No.**	**%**	
Pregnancy	72	0.2	5	0.4	0.0971
Infectious diseases	15,176	35.7	851	61.3	<0.0001*
Major trauma	1,246	2.9	33	2.4	0.2253
Major spine trauma	421	1.0	9	0.7	0.2020
Major extremity trauma	851	2.0	24	1.7	0.4712
Major surgery	9,653	22.7	787	56.7	<0.0001*
CNS	453	1.1	14	1.0	0.8357
Thorax	4,263	10.7	295	21.3	<0.0001*
Abdomen	5,680	13.4	571	41.1	<0.0001*
Urogenital	1,372	3.2	75	5.4	<0.0001*
Orthopedic	162	0.4	2	0.1	0.1539
Hospitalization	13,254	31.2	625	45.0	<0.0001*
Blood transfusion	3,410	8.0	205	14.8	<0.0001*
Active therapy	8,899	21.0	448	32.3	<0.0001*
Chemotherapy only	5,011	11.8	374	27.0	<0.0001*
Radiation only	206	0.5	11	0.8	0.1082
Hormone therapy only	3,158	7.4	38	2.7	<0.0001*
Combination therapy	524	1.2	25	1.8	0.0614
Use of erythropoietin stimulating agent (ESA)	809	1.9	21	1.5	0.2915
Use of granulocyte colony-stimulating factor (GCSF)	1,254	3.0	59	4.3	0.0052*
Thalidomide therapy	26	0.1	0	0.0	1.0000

* p-value < 0.05

5.4.1.2 VTE (Definition 2)

As shown in Table 5.7, mean age (± SD) of cancer patients with VTE (definition 2) was 60.9 years (± 14.3 years), which were significantly older than cancer patients without VTE (59.5 ± 15.9 years). Gender distribution was not significantly different between two patient groups. Compared with cancer patients without VTE event, more cancer patients with VTE events had prior histories of VTE within 2 years before index date (1.1% versus 0.2%, $p < 0.0001$). Furthermore, patients with VTE events were significantly more likely to have comorbid disease (including hypertension, heart failure, ischemic heart disease, renal insufficiency, liver disease, rheumatologic diseases, arterial embolism, obesity, and varicose veins of lower extremities) than patients without VTE event.

Comparison of potential risk factors for development of VTE between patients with and without VTE events is shown in Table 5.8. There was no difference in the prevalence of pregnancy and major trauma. Compared with patients without VTE event, more patients with VTE received major surgery, active therapy, and G-CSF, or diagnosed with infectious diseases within 3 months before/during the VTE event or end of follow-up date. Hospital admission was more frequent in patients with VTE events (60.0% versus 32.1%, $p < 0.0001$). Among patients who received active therapy, more patients with VTE received chemotherapy (38.5% versus 11.9%, $p < 0.0001$) and

combination therapy (4.2% versus 1.2%, $p < 0.0001$), but more patients without VTE received hormone therapy (7.3% versus 3.6%, $p < 0.0001$).

Table 5.7: Baseline characteristics of the study population (VTE definition 2)

	Patients without VTE N = 43,382		**VTE (definition 2) N = 473**		**P-value**
Mean age (years)	59.52 ± 15.92		60.86 ± 14.26		0.0440*
	No.	**%**	**No.**	**%**	
Age groups (years)					0.0005*
≤ 18	502	1.2	1	0.2	
19 – 40	4431	10.2	36	7.6	
41 – 60	16847	38.8	179	37.9	
61 – 80	18183	41.9	227	48.0	
≥ 81	3419	7.9	30	6.3	
Gender					0.3695
Male	22,856	52.7	259	54.8	
Female	20,526	47.3	214	45.2	
Prior history of VTE	67	0.2	5	1.1	0.0011*
Hypertension	15,981	36.8	223	47.2	<0.0001*
Heart failure	1,793	4.1	31	6.6	0.0087*
Ischemic heart disease	6,005	13.8	86	18.2	0.0066*
Atrial fibrillation	649	1.5	9	1.9	0.4522
Renal insufficiency	3,270	7.5	53	11.2	0.0027*
Chronic lung disease	8,211	18.9	95	20.1	0.5229
Diabetes mellitus	7,874	18.2	97	20.5	0.1861
Stroke	2,690	6.2	30	6.3	0.8988
Degenerative & paralytic neurologic disease	3,665	8.5	47	9.9	0.2474
Rheumatologic diseases	573	1.3	12	2.5	0.0218*
Liver disease	7,959	18.4	119	25.2	0.0001*
Arterial embolism	165	0.4	7	1.5	0.0028*
Anemia	5,179	11.9	62	13.1	0.4354
Varicose veins of lower extremities	170	0.4	5	1.1	0.0418*
Peripheral vascular disease	515	1.2	9	1.9	0.1543
Obesity	146	0.3	5	1.1	0.0243*

* p-value < 0.05

Table 5.8: Potential risk factors for development of VTE (VTE definition 2)

	Patients without VTE N = 43,382		**VTE (definition 2) N = 473**		**P-value**
	No.	**%**	**No.**	**%**	
Pregnancy	74	0.2	2	0.4	0.1979
Infectious diseases	15,809	36.4	242	51.2	<0.0001*
Major trauma before VTE event	1260	2.9	18	3.8	0.2465
Major spine trauma	426	1.0	6	1.3	0.4775
Major extremity trauma	861	2.0	12	2.5	0.3924
Major surgery before VTE event	10,152	23.4	286	60.5	<0.0001*
CNS	457	1.1	8	1.7	0.1779
Thorax	4,706	10.9	158	33.4	<0.0001*
Abdomen	6,094	14.1	167	35.3	<0.0001*
Urogenital	1,397	3.2	43	9.1	<0.0001*
Orthopedic	164	0.4	1	0.2	1.0000
Hospitalization	13,909	32.1	284	60.0	<0.0001*
Blood transfusion	3,665	8.5	49	10.4	0.1376
Active therapy	9,079	20.9	221	46.7	<0.0001*
Chemotherapy only	5,151	11.9	182	38.5	<0.0001*
Radiation only	214	0.5	2	0.4	1.0000
Hormone therapy only	3,180	7.3	17	3.6	0.0020*
Combination therapy	534	1.2	20	4.2	<0.0001*
Use of erythropoietin stimulating agent (ESA)	828	1.9	9	1.9	0.9926
Use of granulocyte colony-stimulating factor (GCSF)	1,282	3.0	41	8.7	<0.0001*
Thalidomide therapy	27	0.1	0	0.0	1.0000

* p-value < 0.05

5.4.2 Multivariate Logistic Regression – Risk Factors for VTE

The results of multivariate logistic regression analysis are shown in Table 5.9. Primary cancer sites of GI, brain, lung, gynecologic and renal (OR 1.63, 95% CI 1.32-2.02) and prior history of VTE (OR 4.32, 95% CI 1.60-11.66) were associated with higher risk of VTE. Comorbid diseases, including hypertension (OR 1.41, 95% CI 1.17-1.70), arterial embolism (OR 2.96, 95% CI 1.31-6.67), obesity (OR 2.88, 95% CI 1.13-7.35), and rheumatologic diseases (OR 1.90, 95% CI 1.05-3.43) were all significantly associated with greater risk of VTE in cancer patients.

We also identified major surgery as a significant risk factor for VTE, including thoracic (OR 2.35, 95% CI 1.91-2.89), abdominal (OR 1.99, 95% CI 1.62-2.45), and urogenital surgery (OR 2.12, 95% CI 1.52-2.94). In our models, patients receiving chemotherapy (OR 3.61, 95% CI 2.95-4.41) or combination therapy (OR 4.95, 95% CI 3.08-7.96) were significantly with higher risk of VTE. In contrast, blood transfusion was associated with reduced risk of VTE (OR 0.56, 95% CI 0.42-0.77).

Table 5.9 Multivariate analysis of risk factors for VTE

Variable	Parameter estimate	Standard error	Chi-square	P-value	Odds ratio	95% Cl
Cancer sites						
Low risk (referent)						
High risk	0.486	0.112	18.881	<0.0001*	1.63	1.31 - 2.02
Hematologic	0.230	0.239	0.926	0.3359	1.26	0.79 - 2.00
Prior history of VTE	1.463	0.507	8.326	0.0039*	4.32	1.60 - 11.66
Comorbid diseases						
Hypertension	0.347	0.095	13.378	0.0003*	1.41	1.17 - 1.70
Arterial embolism	1.084	0.415	6.818	0.0090*	2.96	1.31 - 6.67
Obesity	1.059	0.478	4.917	0.0266*	2.88	1.13 - 7.35
Rheumatologic diseases	0.642	0.302	4.519	0.0335*	1.90	1.05 - 3.43
Potential risk factors						
Surgery						
Thoracic surgery	0.855	0.105	65.976	<0.0001*	2.35	1.91 - 2.89
Abdominal surgery	0.689	0.105	43.293	<0.0001*	1.99	1.62 - 2.45
Urogenital surgery	0.751	0.168	19.962	<0.0001*	2.12	1.52 - 2.94
Chemotherapy	1.282	0.103	156.345	<0.0001*	3.61	2.95 - 4.41
Combination therapy	1.600	0.242	43.572	<0.0001*	4.95	3.08 - 7.96
Blood transfusion	-0.571	0.157	13.277	0.0003*	0.57	0.42 - 0.77

* p-value < 0.05

5.5 Treatment Pattern of VTE

5.5.1 Initial Treatment of VTE

5.5.1.1 VTE (Definition 1)

The initial treatment of VTE during the hospital admission was summarized in Table 5.10. Among 1,388 patients with VTE events (definition 1), only 467 patients (33.6%) received anticoagulant therapy or surgical thromboectomy during the hospitalization. Seven patients (0.5%) received thromboectomy during the hospitalization, of whom, 4 patients received thromboectomy alone, and 3 patients received both thromboectomy and IV/SC anticoagulants. Four hundred and eleven patients (29.6%) received LMWH/UFH for initial treatment of VTE, as follow, 201 patients (14.5%) received LMWH, 151 patients (10.9%) received UFH, and 59 patients (4.3%) received both UFH and LMWH. Forty-nine patients (3.5%) received warfarin alone. Only 58 patients (7.9%) with thrombosis of hepatic, portal, or renal vein alone (n=734) received anticoagulation or surgical thromboectomy. Excluding patients with superficial vein thrombosis (n=4), anticoagulation or surgical thromboectomy was performed in 409 patients (62.9%) with other sites of venous thrombosis or PE (n=650).

Anticoagulation or surgical thromboectomy was not performed in 921 patients (66.4%). Of these patients, 676 patients (73.4%) had intra-abdominal venous thrombosis alone (including thrombosis of renal vein, hepatic vein, and portal vein), 38

patients (4.1%) had PE, and 52 patients (5.6%) had thrombosis of extremities. Besides, 26 (2.8%), 109 (11.8%), and 16 (1.7%) patients had thrombosis of vena cava, other unspecified site, and multiple thrombotic sites, respectively. Four patients (0.4%) had thrombosis of superficial vein.

5.5.1.2 VTE (Definition 2)

As shown in Table 5.10, 7 patients (1.5%) received thromboectomy for initial treatment of VTE during the hospitalization, of whom, 4 patients received thromboectomy alone, and 3 patients received both thromboectomy and IV/SC anticoagulants. Among 466 patients who received LMWH/UFH as initial treatment of VTE, 212 patients (45.5%) received LMWH, 192 patients (41.2%) received UFH, and 62 patients (13.3%) received both UFH and LMWH during the hospitalization.

Table 5.10 Initial treatment of VTE during the hospital admission for VTE

	VTE (definition 1) (N = 1,388)	VTE (definition 2) (N = 473)
Treatment	**Patient No. (%)**	**Patient No. (%)**
Thromboectomy	7 (0.5)	7 (1.5)
Low molecular weight heparin (LMWH)		
LMWH only	58 (4.2)	64 (13.5)
LMWH + warfarin	143 (10.3)	148 (31.3)
Unfractioned heparin (UFH)		
UFH only	79 (5.7)	115 (24.3)
UFH + warfarin	72 (5.2)	77 (16.3)
UFH + LWMH		
UFH + LMWH only	16 (1.1)	17 (3.6)
UFH + LMWH + warfarin	43 (3.1)	45 (9.5)
Warfarin only	49 (3.5)	0 (0.00)
No anticoagulation therapy	921 (66.4)	0 (0.00)

5.5.2 Long-term Treatment of VTE

Among 473 patients who hospitalized with VTE (definition 2) between 2001 and 2009, 58 patients (12.3%) did not have any medical claim in the databases after the VTE event. We therefore explored use pattern of long-term anticoagulant treatment in the remaining 415 patients.

Overall, long-term anticoagulant therapy was initiated in 266 patients (64.1%) (Table 5.11), as follows: LMWH alone in 24 patients (5.8%), UFH alone in 24 patients (5.8%), warfarin alone in 192 patients (46.3%), LMWH and warfarin in 13 patients (3.1%), UFH and warfarin in 10 patients (2.4%), and LMWH and UFH in 3 patients (0.7%). The median duration of anticoagulant therapy was 66 days (range, 2-1442 days).

As shown in Table 5.12, 58.7%, 18.4%, 13.5% and 9.4% of patients received ≤ 3 months, 3-6 months, 6-12 months and ≥ 12 months of long-term anticoagulant therapy, respectively.

Table 5.11 Anticoagulants administered during long-term treatment

	Total patient (N=415)	
Anticoagulants	**N**	**%**
LMWH alone	24	5.8
UFH alone	24	5.8
Warfarin alone	192	46.3
LMWH and warfarin	13	3.1
UFH and warfarin	10	2.4
LMWH and UFH	3	0.7
No anticoagulant therapy	149	35.9

Table 5.12 Duration of long-term anticoagulant therapy

	Total patient (N=266)	
Treatment duration	**N**	**%**
≤ 3 months	156	58.7
3 – 6 months	49	18.4
6 – 12 months	36	13.5
≥ 12 months	25	9.4

5.6 Recurrence of VTE and Bleeding Complications

5.6.1 Recurrence of VTE

Of 415 patients, 81 patients (19.5%) had recurrence of VTE after the first hospitalization for VTE event. Twelve VTE recurrence events (14.8%) occurred among patients who did not received any anticoagulant for long-term treatment of VTE. Forty VTE recurrence events (49.4%) occurred during anticoagulant therapy and 29 recurrence events (35.8%) occurred after discontinuation of anticoagulant therapy.

Median time to recurrence of VTE was 55 days (range, 5-2,193 days). The cumulative rates of VTE recurrence at 30, 90, 180 and 365 days were 5.5%, 13.7%, 15.7%, and 16.9%, respectively (Table 5.13). Approximately 70% of recurrent VTE (n=57) occurred within 90 days after the first VTE event. No significant difference between the warfarin group and the LMWH/UFH group was detected in the rate of VTE recurrence (13.5% versus 19.6%, p-value = 0.28) (Table 5.14).

Table 5.13 Cumulative rates of VTE recurrence

Time to recurrence of VTE	Patient No.	Cumulative rate of VTE (%)
≤ 30 days	23	5.5
31 – 90 days	34	13.7
91 – 180 days	8	15.7
181 – 365 days	5	16.9
> 365 days*	11	19.5

* The last observed event occurred at 2,193 days after the first VTE event

5.6.2 Bleeding Complications

As shown in Table 5.14, during long-term anticoagulant treatment of VTE, intracranial or GI bleeding events occurred in 19 patients (9.9%) who received warfarin and 5 patients (11.8%) who received LMWH/UFH. Among patients who did not received long-term anticoagulant treatment, 27 patients (18.1%) had bleeding events. Five intracranial bleeding events (1.2%) occurred in our study cohort. Of these, 3 events occurred among patients who did not received long-term anticoagulant treatment and 2 events occurred among patients who received warfarin for long-term treatment of VTE. No patients in LMWH/UFH group developed intracranial bleeding. No significant difference between the warfarin group and the LMWH/UFH group was detected in the rate of bleeding event (9.9% versus 11.8%, p-value = 0.70).

Table 5.14 Recurrence of VTE and bleeding complications during long-term anticoagulant treatment

Anticoagulant	Total patient N = 415	VTE recurrence N (%)	Bleeding events N (%)
No anticoagulant	149	12 (8.1%)	27 (18.1%)
Warfarin	192	26 (13.5%)	19 (9.9%)
LMWH/UFH	51	10 (19.6%)	5 (11.8%)
Warfarin and LMWH/UFH	23	4 (17.4%)	2 (8.7%)

Chapter 6 Discussion

6.1 Baseline Characteristics of Study Cohort

The median age of men and women in our study cohort were 64 years and 56 years respectively, and the sex ratio of men to women is 1.11. This is consistent with the reports of Cancer Registry Annual Report Year 2008 of Taiwan published in year 2010. The reported median age of men and women were 65 years and 59 years, respectively, with a sex ratio of 1.33. The five leading cancers in our study cohort were the same as reported in the Cancer Registry Annual Report, which were colorectal cancer, breast cancer, liver cancer, head and neck cancer, and lung cancer, but with higher frequency of head and neck cancer in our cohort.

In our study, admission date of the first hospitalization with a primary diagnosis of malignant disease was defined as the newly cancer diagnosed date. In order to defined the newly cancer diagnosed date more precisely, we check their outpatient claims 1 year prior to newly cancer diagnosed date. We found that only 18,242 patients (41.6%) had any outpatient claim with a primary diagnosis of malignant disease within 1 year before newly cancer diagnosed date. Among these patients, the median time of the first outpatient claim with primary diagnosis of malignant disease to newly cancer diagnosed date was 11 days. Therefore, we believed that adopting the admission date of first hospitalization with a primary diagnosis of malignant disease as the newly cancer

diagnosed date is suitable.

6.2 Incidence Rate of VTE among Cancer Patients

Given the relatively low incidence rate of various types of cancer and VTE among Asian population, a large cohort study is needed to estimate the incidence rate of VTE across different cancer types. Use of Taiwan NHI research database has been proved to be a powerful data source for epidemiological studies of rare diseases.[91-94] Using the NHI research database, we examined the incidence, risk factors and clinical characteristics of VTE among patients with different cancer types over a period of 9 years.

Two definitions of VTE were adopted in our study. To verify the accuracy of diagnosis, VTE (definition 2) was based on both the VTE diagnosis codes and management of VTE during the hospital stay. This definition was similar to the outcome definition used in the population-based studies of Lee *et al.*[10] and Jang *et al.*[8], which used Taiwan and Korea NHI databases as data source to explore the epidemiology of VTE among the general population. However, cancer patients have more thrombosis at unusual sites than the general population, such as thrombosis of upper extremities, vena cava, and splanchnic veins.[55] The application of anticoagulants has not been confirmed in these situations.[75] Some cancer patients who diagnosed with thrombosis of upper

extremities, splanchnic veins, and other unspecified site may not receive anticoagulant treatment. Therefore, patients with thrombosis at unusual sites might not be included as VTE cases according to definition 2. To avoid serious underestimation of the incidence rate of VTE among cancer patients, we defined VTE event as hospitalization with any diagnosis of VTE in the inpatient medical claims (definition 1). We use two outcome definitions in our study to provide a crude incidence rate of VTE which included accidentally detected VTE and clinical symptomatic VTE.

In our study, 1.1% to 3.2% of all newly diagnosed cancer patients were hospitalized for VTE events. The incidence rate of VTE (definition 1 and definition 2) were 9.88 per 1,000 person-years (range, 1.0-68.2 per 1,000 person-years) and 3.35 per 1,000 person-years (range, 0.0-16.0 per 1,000 person-years), respectively (Table 5.1 and 5.2). The incidence rate of VTE is 21- to 62- folds among cancer patients than the general population (15.9 per 100,000 person-years).[10] Malignancy alone was reported to be associated with 4-folds increased risk of VTE and the use of chemotherapy increased the risk to 6.5-folds. Meanwhile, surgery and hospital admission were associated with 21-folds and 8-folds increased risk of VTE, respectively.[34] There is convincing evidence that the risk of VTE increases in proportion to the number of predisposing factors.[32,33] Taken together, these conditions may contribute to the high incidence rate of VTE among cancer patients.

The higher incidence rate of VTE in our study may also be partially explained by the differences in the outcome definition and studied year in different studies. For example, Lee *et al.*[10] did not include diagnosis of phlebitis and thrombophlebitis (ICD9-CM codes 451.xx) in their study and they only included patients with VTE events between 2001 and 2002. In contrast, we used more recent data, including patients with VTE events between 2001 and 2009. In addition, ICD9-CM codes of VTE used in our study included 451.xx-453.xx.

Incidence rates of VTE among Asian cancer patients have been studied in certain types of cancer associated with higher risk of VTE, including colorectal cancer (4.5%),[15] gastric cancer (3.5%),[14] advanced pancreatic cancer (5.3%),[12] diffuse large B cell lymphoma (10.6%),[16] multiple myeloma (3.9%),[13] and cholangiocarcinoma (3.7%)[18] (Table 2.9). Our reported rates are lower than the rates reported in previously disease-specific studies among Asian population.[12-16,18] Data sources used in our study and previous studies may result in these differences. All existing studies used medical records database as data source and most of them defined outcomes as objectively confirmed VTE events (including accidentally detected VTE). In our study, some accidentally detected VTE during imaging studies for assessment of tumor status or other diseases might not be recorded in the NHI claim-based databases.

The inclusion criteria of patients in different studies might be another contributing factor. Koh *et al.*[13] only included patients with multiple myeloma who receiving thalidomide therapy and Oh *et al.*[12] only included patients with unresectable advanced pancreatic cancer in their studies. In the study of Yokoyama *et al.*[16], 72% of patients had stage III/IV diffuse large B cell lymphoma. More advanced stage diseases among their study populations and the use of thalidomide therapy can explain the higher incidence rate of VTE compared with our study. In patients with multiple myeloma, VTE rates of 28% had been reported in patients treated with thalidomide-based chemotherapy regimens.[80]

The incidence of VTE varies in different ethnic populations. Risk of developing VTE is reported to be significantly lower among Asian populations than Caucasian populations.[22,26,27] Among Caucasian patients with cancer, the estimated incidence rate of VTE ranges from 0.6% to 12.1% (Table 2.3 and 2.4).[47-54] In our study, the incidence rate of VTE (definition 2) (1.1%) is about 2-folds lower than that reported in study in Denmark (1.8%) using administrative database[52] and 4-folds lower than another study in USA (4.0%) using discharge database of the University HealthSystem Consortium as data source.[51] The incidence rate of VTE (definition 1) (3.2%) was similar to the rate reported by Khorana et al. among Asians/Pacific Islanders patients in 2007 (3.3%).[51] In general, the incidence rates of VTE in Asian populations were lower than existing

studies among Caucasian populations.

The rates of VTE (definition 2) varied with various malignancies from 0.5 per 1,000 patient-years in patients with thyroid cancer to 16.0 per 1,000 patient-years in patients with pancreas cancer (Table 5.2). We found that pancreas cancer, lung cancer, liver cancer, multiple myeloma, and sarcoma were associated with higher rates of VTE, which are consistent with other researches.[49,51,52,54] Pancreas cancer and multiple myeloma have been associated with high risk of VTE.[49,51,52] Higher VTE risks in patients with lung and liver cancer were also found in our study.

6.3 Clinical Characteristic of VTE

In our study, 70.8% (definition 1) and 59.4% (definition 2) of VTE events occurred within 1 year after the first diagnosis of cancer, with 35.8% (definition 1) and 18.0% (definition 2) of events occurred at index date (Table 5.3). In a retrospective study based on California cancer registry, 12% of VTE events were diagnosed at the time cancer was diagnosed.[5] The highest risk of VTE in the initial period after the diagnosis of cancer is consistent with other studies.[1,5-7,52,59,62]

Thrombosis of portal vein is common in our study. Among patients with VTE, 51.5% (definition 1) and 18.2% (definition) of patients had portal vein thrombosis alone (Table 5.4). More than 80% of the portal vein thrombosis occurred in patients with primary diagnosis of liver cancer. Infectious diseases, inflammatory abdominal foci, and malignant conditions of abdominal (including gastric, pancreatic, and liver cancer) are well-known risk factors for portal vein thrombosis.[95,96] Malignancies, especially liver or pancreas cancer, are responsible for 21% to 24% of overall cases of portal vein thrombosis.[96] Liver cancer is the third common cancer in Taiwan and the most common cause of cancer death each year.[97] The high prevalence of liver cancer in Taiwan may result in the high prevalence of portal vein thrombosis in our study cohort.

6.4 Risk Factors for VTE

In multivariate logistic regression models, cancer site, prior history of VTE, hypertension, arterial embolism, obesity, rheumatologic diseases, major surgery, chemotherapy, and combination therapy were significantly associated with higher risk of VTE (Table 5.9). Several risk factors, including arterial embolism,[51] obesity,[46,50,51] and chemotherapy[48,51,52,98] were also reported in previous studies. Consistent with previous studies, [48,50,51,53,54] we also found that cancer of GI tract, brain, lung, gynecology, and liver were significantly associated with higher risk of VTE when compared with other solid tumors.

Prior history of VTE is an important risk factor for VTE.[99,100] In a prospective study on VTE after cancer surgery, previous VTE history was a significant risk factor for VTE.[57] In our study, prior history of VTE was defined as being hospitalized with VTE diagnosis within 2 years before index date. The definition of prior history of VTE based on appearance of VTE diagnosis in inpatient claims is consistent with previous studies in Taiwan based on NHIRD.[10,101]

Although the association of hypertension and development of VTE has been limited in cancer patients,[50] hypertension had been identified as an independent risk factor for VTE in antiphospholipid antibody carriers.[102] It was also found that hypertension was associated with increased risk of PE in a study of 112,822 women based on biennial,

mailed questionnaires.[103] In a meta-analysis of association between cardiovascular risk factors and VTE, patients with hypertension had higher risk of VTE (OR 1.51; 95% CI 1.23-1.85).[104] From a laboratory perspective, an association between venous and arterial events is plausible because they share common characteristics such as activation of platelets and coagulation.[104]

Rheumatologic diseases were first identified as an independent risk factor for VTE among cancer patients in our study. Rheumatologic diseases were not found to be risk factors for VTE in previous studies.[42,105] However, recent epidemiological studies suggested that certain rheumatologic diseases, including rheumatic arthritis (RA),[106,107] dermatomyositis/polymyositis and systemic lupus erythematous (SLE) were associated with increased risk of VTE.[106] Changes in expression of selectins and cellular adhesion molecules of vessel endothelium induced by inflammation may contribute to the initiation of venous thrombus formation.[106]

Many cancer therapies (including surgery, chemotherapy, antiangiogenic, and hormone therapy) place cancer patients at greater risk for VTE. The risk of postoperative VTE in cancer patients exceeds that of non-cancer surgical patients by 2- to 3-folds.[55] Without perioperative thromboprophylaxis, reported incidence of proximal-vein thrombosis and PE can be as high as 10-20% and 1-5%, respectively.[1] Our study found that major thoracic (OR 2.35, 95% CI 1.91-2.89), abdominal (OR 1.99,

95% CI 1.62-2.45), and urogenital surgery (OR 2.12, 95% CI 1.52-2.94) is significantly associated with higher risk of VTE. Furthermore, chemotherapy (OR 3.61, 95% CI 2.95-4.41) and combination therapy (OR 4.95, 95% CI 3.08-7.96) were also significant risk factors for VTE.

In addition to cancer therapy, certain supportive care used in cancer patients also appears to increase the risk of VTE. Khorana *et al.*[51,108] found that both red blood cell and platelet transfusions are associated with increased risks of venous thrombotic events in hospitalized patients with cancer. However, our study showed conflicting result that transfusion of blood and blood components was associated with reduced risk of VTE. Further investigations are needed to confirm the association of blood transfusion and VTE among cancer patients.

When the potential risk factors were recorded during the same hospitalization with VTE admission, the causal relationship between the exposure to potential risk factors and the development of VTE may be uncertain. Therefore, we conducted a sensitivity analysis which included potential risk factors that documented in inpatient or outpatient claims within 3 months before VTE event/end of follow up date only. The result of the multiple logistic regression analysis was shown in Table 6.1. Primary cancer sites of GI tract, brain, lung, gynecologic and renal, prior history of VTE, hypertension, arterial embolism, obesity, abdominal surgery, chemotherapy, and combination therapy are

significantly associated with greater risk of VTE in cancer patients. Besides, comorbid renal failure and hospitalization ≥ 3 days within 3 months are also significant risk factors for VTE. In contrast, blood transfusion was significantly associated with reduced risk of VTE. The identified risk factors are consistent with previous studies.[50,51,100]

Table 6.1 Sensitivity analysis of risk factors for VTE

Variable	Odds ratio	95% CI	P-value
Cancer sites			
Low risk (referent)			
High risk	1.78	1.44 - 2.22	<0.0001
Hematologic	1.51	0.95 - 2.39	0.0823
Prior history of VTE	4.67	1.80 - 12.09	0.0015
Comorbid diseases			
Hypertension	1.38	1.14 - 1.66	0.0008
Renal failure	1.40	1.04 - 1.87	0.0273
Arterial embolism	2.91	1.32 - 6.43	0.0080
Obesity	3.31	1.33 - 8.21	0.0100
Potential risk factors			
Abdominal surgery	1.32	1.03 - 1.69	0.0309
Chemotherapy	1.99	1.58 - 2.51	<0.0001
Combination therapy	3.89	2.36 - 6.39	<0.0001
Hospitalization ≥ 3 days	2.23	1.78 - 2.79	<0.0001
Blood transfusion	0.28	0.17 - 0.48	<0.0001

6.5 Initial Treatment Pattern of VTE

Among patients who were hospitalized with VTE diagnosis (definition 1), only 33.6% of patients received anticoagulants or surgical thromboectomy during the hospitalization. Treatment for VTE was performed in 7.9% and 62.9% of patients with intra-abdominal thrombosis and other sites of venous thrombosis/PE (excluding superficial venous thrombosis), respectively.

In a retrospective study in patients with gastric cancer, anticoagulant therapy was administered to 38% of patients.[14] Anticoagulant therapy was performed in most of the DVT/PE cases (86%), but only in 8% of the intra-abdominal thrombosis cases (including portal vein, hepatic vein, renal vein, inferior vena cava, and internal iliac vein).[14] Similarly, in the study of Choi et al,[15] which included 2,006 patients with colorectal cancer, anticoagulant therapy was administered in 53% of patients with VTE. Although anticoagulation was administered to most patients with DVT/PE (91%), only 15% of patients with intra-abdominal thrombosis received anticoagulant therapy.[15]

Consistent with previous studies,[14,15] we observed that most patients with thrombosis of renal, portal or hepatic veins did not received anticoagulant treatment in clinical practice. The recently published 9th ACCP guidelines in 2012 suggested therapeutic anticoagulation to patients with symptomatic splanchnic vein thrombosis but not patients with incidentally detected splanchnic vein thrombosis.[75] However, due to

limited understanding of the natural histories of both symptomatic and incidentally detected splanchnic vein thrombosis in patients who are not treated with anticoagulants (ie., frequency of bowel infarction, development of portal hypertension, recurrence), a paucity of data from prospective cohort studies, and a lack of randomized trials of standardized anticoagulant therapy for splanchnic vein thrombosis, the role of anticoagulation for this condition is uncertain.[75] Given the common prevalence of intra-abdominal thrombosis, further studies are needed to clarify the role and duration of anticoagulant therapy in these patients.

6.6 Long-term Treatment of VTE

Our study found that the adherence to treatment guidelines was poor in Taiwan. Long-term anticoagulant therapy was only initiated in 64.1% of patients (definition 2). In treatment guidelines, 3-6 months of LMWH was recommended over warfarin for long-term treatment of VTE in cancer patients.[1,69,70,75] However, in our study, among patients who received long-term treatment of VTE, LMWH was administered to 15.0% of patients only at any time. Most patients received warfarin monotherapy for the long-term treatment of VTE (72.2%) (Table 5.11).

In contrast, in the study of Trujillo-Santos et al. (2008)[109], long-term LMWH monotherapy was administered to 53.3% of cancer patients. Among cancer patients with VTE, 46.8% of them received warfarin for long-term treatment.[109] In the study of Lee *et al.*[14] and Choi *et al.*[15], long-term LMWH monotherapy and warfarin was performed in 71.1% versus 28.9% of patients, and 66.7% versus 33.3% of patients, respectively. The clinical studies of long-term treatment of VTE among cancer patients were summarized in Table 6.2. In Taiwan, most patients use warfarin instead of LMWH monotherapy for long-term treatment of VTE. This is probably because reimbursement for outpatient use of LMWH by NHI was limited to pregnant patients with prosthetic valve replacement.[101]

Furthermore, in our study, treatment duration of long-term anticoagulant therapy was shorter than those recommended in clinical guidelines.[1,69,70,75] Instead of recommendation of long-term treatment for 3-6 months, more than half of the patients (58.7%) in our study received long-term anticoagulant therapy for less than three months (Table 5.12). The median duration of long-term anticoagulant therapy was 66 days, which is also shorter than the median duration recorded in the study of Lee *et al.*[14] and Choi *et al.*[15] (85 days and 90 days, respectively).

Table 6.2 Clinical studies of long-term treatment of VTE among cancer patients

Study	LMWH (%)	VKA (%)	Median duration (days)
Our study	15.0[a]	72.2	66
Lee et al. (2010)[14]	71.1	28.9	85
Choi et al. (2011)[15]	66.7	33.3	90
Trujillo-Santos et al. (2008)[109]	53.3	46.8	NA[b]

[a] Use of LMWH at any time

[a] Not available

6.7 Recurrence of VTE and Bleeding Complications

Use of administrative database to evaluate the recurrence of VTE has been scarce. Due to the limitations of NHI database, we could not assess radiographs of patients to verify the recurrence of VTE. Therefore, we defined recurrent VTE as a second hospitalization with a diagnosis of VTE and treatment with IV/SC anticoagulant therapy or thromboectomy during the hospital stay after the first hospital admission for VTE, as proposed by Lee *et al*.[10] In that study, Lee *et al*.[10] used Taiwan's NHI database to explore the incidence and cumulative recurrence rates of VTE among general population.

In our study, 19.5% of patients had recurrent VTE after the first hospitalization for VTE event. In a prospective study which included 842 patients, Prandoni *et al*.[66] reported that cancer patients were 4 times more likely to develop recurrent VTE compared to general population. However, the proportion of patients with recurrent VTE in our patients was only slightly higher than the recurrence rates reported by Lee *et al*[10] among general population (19.5% versus 14.4%).

Four clinical trials enrolling cancer patients with VTE found that, compared to treatment with VKA, three to six months of LMWH was associated with fewer VTE recurrence or fewer bleeding events.[76-79] Cochrane meta-analysis also showed that, long-term treatment with LMWH, compared with VKA, provided significantly

reduction in recurrence of VTE.[110] In our study, there is no significant difference in the rate of recurrent VTE and bleeding event between the warfarin and LMWH/UFH group. However, long-term treatment with warfarin may cause more fatal bleeding events than LMWH/UFH. In our study, 2/5 of intracranial bleeding events occurred in patients receiving warfarin alone for long-term treatment of VTE. In contrast, no intracranial bleeding event occurred in LMWH/UFH group.

In our study, we only evaluate GI and intracranial bleeding complications. The definition of GI bleeding in our study was same as Chang et al.,[111,112] which used Taiwan NHI databases to evaluate GI adverse events associated with nonsteroidal anti-inflammatory drugs (NSAIDs). Common sites for anticoagulant-associated bleeding including soft tissues, the GI and urinary tract, the nose and the oral pharynx.[113] Rate of fatal bleeding ranged from 0.1-1.0% patient-years.[114] In the Computerized Registry of Patients with Venous Thromboembolism (RIETE) registry, among 3,805 cancer patients with VTE events, 4.1% of patients developed major bleeding. The most common bleeding sites were GI tract (47%), genitourinary (19%), and brain (8.3%).[109] As GI bleeding is the most common bleeding complications of anticoagulant therapy,[109] the risk of GI bleeding has an important influence on clinical practice in Asian countries,[115] and intracranial bleeding resulting in hemorrhagic stroke represents the most common cause of fatal bleeding associated with anticoagulants,[113]

we only focused on GI and intracranial bleeding complications in our study. Besides, validation studies using administrative healthcare databases in Canada and Italy reported that use of ICD-9-CM codes to identify upper GI bleeding had a positive predictive value of 90%.[116,117]

6.8 Strengths of Our Study

This study represents the largest national population-based epidemiologic study in Asia which first described the management of VTE among cancer patients in real world in Taiwan. In this study, we revealed the inconsistency of real world practice and clinical guidelines. The reimbursement for LMWH by NHI may have a great impact on clinical practice. Besides, two outcome definitions were adopted in our study. We believed that we provide a crude incidence rate of VTE among cancer patients which included both accidentally detected VTE and clinical symptomatic VTE.

6.9 Limitations

Some limitation may be pointed out in the present study, generally related to the use of claim database. First, the definition of outcomes in our study is based on diagnostic codes of administrative database. However, the accuracy of coding for VTE has been previously validated and is considered to be accurate.[118-120] Second, other factors that may contribute to development of VTE, including smoking status, disease stage, indwelling catheter, laboratory data, body weight, and international normalized ratio (INR) could not be obtained from the databases. Third, the actual incidence of VTE may be underestimated, because some patients with PE die suddenly without accurate diagnosis and some patients with accidentally detected VTE may not be documented.

However, we believed that we provide the incidence rate of clinically overt VTE, which is useful in helping decision making of VTE prophylaxis in clinical practice.

Fourth, we are unable to provide the actual incidence rate of recurrent VTE and bleeding events, because some events may be not documented in the database. Besides, we could not assess radiographs to verify the recurrence of VTE and the exact location of thrombosis. Fifth, the study cohort may have received anticoagulant treatment based on certain baseline and prognostic characteristics. We also could not confirm whether the patients had adhered to the instructions for taking their prescriptions of anticoagulants. This could bias the study findings. Randomized clinical trial is needed to confirm the harms and benefits of treatment with warfarin versus LMWH for VTE among Asian population. Finally, thromboprophylaxis can alter the incidence of VTE, but its use in our study population is unknown.

Chapter 7 Conclusions and Suggestions

In summary, this retrospective cohort study describes the epidemiology and clinical profile of VTE across different types of cancer among an Asian population. Although the incidence rate of cancer-related VTE is lower than Caucasians population, it is much higher than the general Asian population. VTE is not rare in certain cancer including pancreas, liver, lung cancer, and multiple myeloma. Risk factors for VTE include prior history of VTE, arterial embolism, hypertension, obesity, rheumatologic diseases, chemotherapy, combination therapy, and major surgery. The incidence rate of VTE is highest within 1 year after cancer diagnosis.

High incidence rate of VTE was detected among cancer patients in Taiwan. Clinical practitioners should carefully monitor patients with cancer for VTE. Adherence to treatment guidelines was poor in real world. Treatment and prophylaxis of VTE should be optimized, especially in patients with higher-risk of VTE. Due to the different epidemiologic profile of VTE in Taiwan compared with Caucasian population, further investigations are desired to estimate the harms and benefits of anticoagulants treatment and thromboprophylaxis among Asian cancer patients.

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Appendix

Appendix 1 ICD-9-CM codes of comorbid diseases and potential risk factors used in this study

Disease Category	ICD-9-CM Codes
Hypertension (malignant, benign, unspecified)	401.xx-405.xx
401 Essential hypertension	
402 Hypertensive heart disease	
403 Hypertensive renal disease	
404 Hypertensive heart and renal disease	
405 Secondary hypertension	
Heart failure (unspecified, left heart, systolic, diastolic)	428.xx
Ischemic heart disease	410.xx-414.xx
410 Acute myocardial infarction	
411 Other acute and subacute forms of ischemic heart disease	
412 Old myocardial infarction	
413 Angina pectoris	
414 Other forms of chronic ischemic heart disease	
Renal insufficiency	580.xx-589.xx
580 Acute glomerulonephritis	
581 Nephrotic syndrome	
582 Chronic glomerulonephritis	
583 Nephritis and nephropathy not specified as acute or chronic	
584 Acute kidney failure	
585 Chronic kidney disease	
586 Renal failure, unspecified	
587 Renal sclerosis, unspecified	
588 Disorders resulting from impaired renal function	
589 Small kidney of unknown cause	
Chronic lung disease	490-496
490 Bronchitis, not specified as acute or chronic	
491 Chronic bronchitis	
492 Emphysema	
493 Asthma	
494 Bronchiectasis	
495 Extrinsic allergic alveolitis	
496 Chronic airway obstruction, not elsewhere classified	

Appendix 1 ICD-9-CM codes of comorbid diseases and potential risk factors used in this study (continued)

Disease Category	ICD-9-CM Codes
Liver disease	571.2, 571.4x, 571.5,
571.2 Alcoholic cirrhosis of liver	571.6, 572.2-572.8,
571.4 Chronic hepatitis	456.0-456.2x
571.5 Cirrhosis of liver without mention of alcohol	
571.6 Biliary cirrhosis	
572.2 Hepatic encephalopathy	
572.3 Portal hypertension	
572.4 Hepatorenal syndrome	
572.8 Other sequelae of chronic liver disease	
456.0 Esophageal varices with bleeding	
456.1 Esophageal varices without mention of bleeding	
456.2 Esophageal varices in diseases classified elsewhere	
Degenerative and paralytic neurologic disease	438.2x-438.9x,
438.2 Hemiplegia/hemiparesis	330.xx- 337.xx,
438.3 Monoplegia of upper limb	340-349.xx
438.4 Monoplegia of lower limb	
438.5 Other paralytic syndrome	
438.6 Late effects of cerebrovascular disease, alterations of sensations	
438.7 Late effects of cerebrovascular disease, disturbances of vision	
438.8 Other late effects of cerebrovascular disease	
438.9 Unspecified late effects of cerebrovascular disease	
330-337 Hereditary and degenerative diseases of the central nervous system	
340-349 Other disorders of The central nervous system	
Diabetes mellitus	250.xx
Stroke	430-436
430 Subarachnoid hemorrhage	
431 Intracerebral hemorrhage	
432 Other and unspecified intracranial hemorrhage	
433 Occlusion and stenosis of precerebral arteries	
434 Occlusion of cerebral arteries	
435 Transient cerebral ischemia	
436 Acute, but ill-defined, cerebrovascular disease	

Appendix 1 ICD-9-CM codes of comorbid diseases and potential risk factors used in this study (continued)

Disease Category	ICD-9 Codes
Atrial fibrillation	427.31
Anemia	280.x-285.xx
280 Iron deficiency anemias	
281 Other deficiency anemias	
282 Hereditary hemolytic anemias	
283 Acquired hemolytic anemias	
284 Aplastic anemia and other bone marrow failure syndromes	
285 Other and unspecified anemias	
Rheumatologic diseases	710.0, 710.1,
710.0 Systemic lupus erythematosus	710.4, 714.0-714.2,
710.1 Systemic sclerosis	714.81, 725
710.4 Polymyositis	
714.0 Rheumatoid arthritis	
714.1 Felty's syndrome	
714.2 Other rheumatoid arthritis with visceral or systemic involvement	
714.81 Rheumatoid lung	
725 Polymyalgia rheumatica	
Arterial embolism	444.xx
Varicose veins of lower extremities	454.x
Obesity	278.xx
Peripheral vascular disease	441.x, 443.9,
441 Aortic aneurysm and dissection	785.4, V43.4
443.9 Peripheral vascular disease, unspecified	
785.4 Gangrene	
V43.4 Blood vessel replaced by other means	
Pregnancy	640.xx-677
640-649 Complications mainly related To pregnancy	
650-659 Normal delivery, and other indications for care in pregnancy, labor, And delivery	
660-669 Complications occurring mainly in the course of labor and delivery	
670-677 Complications of the puerperium	

Appendix 1 ICD-9-CM codes of comorbid diseases and potential risk factors used in this study (continued)

Disease Category	ICD-9 Codes
Spine fracture	805.xx-806.xx
805 Fracture of vertebral column without mention of spinal cord injury	
806 Fracture of vertebral column with spinal cord injury	
Extremity fracture and dislocation	808.xx-828.xx,
808 Fracture of pelvis	830.xx-839.xx
809 Ill-defined fractures of bones of trunk	
810-819 Fracture of upper limb	
820-829 Fracture of lower limb	
830-839 Dislocation	
Infectious diseases	001.x-139.x,
001-139 Infectious and parasitic diseases	480.xx-488.xx,
480-488 Pneumonia and influenza	590.xx, 680.xx-
590 Infections of kidney	686.xx, 996.6x,
680-686 Infections of skin and subcutaneous tissue	998.5x, 999.3x
996.6 Infection and inflammatory reaction due to internal prosthetic device implant and graft	
998.5 Postoperative infection not elsewhere classified	
999.3 Other infection due to medical care not elsewhere classified	
Blood transfusion	99.0x
Chemotherapy or biologic therapy	V58.1x, V67.2,
V58.1 Encounter for antineoplastic chemotherapy and immunotherapy	00.15, 99.25, 99.28
V67.2 Follow-up examination, following chemotherapy	
00.15 High-dose infusion interleukin-2	
99.25 Injection or infusion of cancer chemotherapeutic substance	
99.28 Injection or infusion of biological response modifier as an antineoplastic agent	
Radiation therapy	V58.0

Appendix 1 ICD-9-CM codes of comorbid diseases and potential risk factors used in this study (continued)

Disease Category	ICD-9 Codes
Major surgery	
• Neurology (operations on skull, brain, cerebral meninges, spinal cord, spinal canal structures, cranial and peripheral nerves, and sympathetic nerves or ganglia)	01.xx-05.xx
• Thorax (operations on larynx, bronchus, lung, chest wall, mediastinum, diaphragm, heart, and peripheral vessels)	30.xx, 32.xx, 33.xx, 35.xx, 36.1x-36.9x, 37.5x, 37.6x, 38.xx-40.xx
• Abdomen(operations on esophagus, stomach, liver, spleen, pancreas, small intestine, large intestine, gall bladder, and biliary tract)	42.xx-54.xx
• Urogenital (operations on kidneys, ureters, urinary bladder, urethra, prostate, seminal vesicles, male genital organs, and female genital organs)	55.xx-71.xx
• Orthopedics (operations on hip replacement, knee replacement, the spine)	81.0x, 81.3x, 81.5x, 81.6x