Original Article

Pharm Sci Asia 2018; 45 (2), 114-122
DOI : 10.29090/psa.2018.02.114

Incidence and risk factors for venous thromboembolism in Thai hospitalized lymphoma patients

W. Kunawuttinankorn[1], K. Tanyasaensook[1], P. Rojnuckarin[2]*
[1] Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand
[2] Division of Hematology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

ARTICLE INFO
Article history:
Received 29 September 2017
Received in revised form
22 December 2017
Accepted 20 January 2017

KEYWORDS:
Venous thromboembolism;
Lymphoma; Thailand;
Hospitalized patients

ABSTRACT

Venous thromboembolism (VTE) is a common complication in cancer patients. However, the magnitude of this problem in Thai hospitalized lymphoma patients has not been well studied. To identify the incidence and risk factors for VTE in those patients, retrospective and prospective cohort studies were conducted in lymphoma patients admitted to a medical school affiliated hospital. Patient profile and risk factors were recorded. Patients were followed up for 90 days after admission. A total of 469 patients were included, of which 422 patients identified from 2007 to 2011 from hospital electronic data base were in the retrospective cohort, and 47 patients enrolled during 6 months in 2012 were in the prospective cohort. Two patients in the retrospective cohort had unconfirmed VTE, and then were excluded. The incidences of VTE in the retrospective cohort and the prospective cohort were 3.6% and 8.5%, respectively (p=0.113). In the retrospective cohort, VTE rates in Non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) patients were 3.4% and 5.9%, respectively (p= 0.347). All VTEs in the prospective cohort were in NHL patients. Concerning time to VTE, all events occurred before starting or during the first 3 courses of chemotherapy. Upon multivariate analysis, the independent risk factor for VTE was being bedridden (adjusted odds ratio 6.21, 95% confidence interval 1.59 – 24.31). In conclusion, the incidence of VTE in Thai hospitalized lymphoma patients admitted for chemotherapy is high. This implies that VTE prophylaxis should be considered during the early courses of chemotherapy in bedridden lymphoma patients.

1. INTRODUCTION

Venous thromboembolism (VTE) results from blood clot formation within veins starting from deep vein thrombosis (DVT) that may progress to potentially fatal pulmonary embolism (PE). It is a common complication in cancer patients. The risk of VTE was 4 to 7-fold increase in cancer patients as compared to patients without cancer[1]. Cancer was also the most common risk factor for VTE in Thai patients[2]. High incidence rates of VTE have been concerned in hospitalized cancer patients and significantly increased among those on chemotherapy[3-5]. Previous western studies reported VTE rates in hospitalized cancer patients ranging from 2 to 4%[3,4,6]. In Thai patients, the incidence of symptomatic

***Corresponding author:** umjung111@yahoo.com

VTE in cancer patients admitted to medical wards without thromboprophylaxis was 1.8%[7]. This was comparable to those western studies. Cancer patients with VTE may have unfavorable consequences, such as high rates of recurrent VTE, bleeding from anticoagulants, prolonged hospitalization, delayed cancer treatment, increased health care costs, increased utilization of health care resources, decreased quality of life, and suffering from post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension[8,9]. Furthermore, those patients appear to have poor survival as cancer patients with VTE had higher a mortality rate than those without VTE[3].

The incidence of VTE varies according to primary sites of cancer[10]. Solid tumors of pancreas, stomach, ovarian, kidney, lung, and brain are strongly associated with higher rates in previous studies. However, many recent studies reported high frequencies of VTE in hematological malignancies which were similar to or even higher than that observed in those solid tumors[1,11-13]. Lymphoma has been considered as a high-risk group of hematological malignancies for developing VTE[11,14]. Several studies reported high incidence of 6.4% to 17.1% of VTE in lymphoma patients that were associated with poor prognosis[15-18]. Pathogenesis of VTE in lymphoma can be explained by three factors: 1. endothelial cell activation due to overexpressed proteins of blood clotting formation on cancer cells; 2. venous stasis from tumor compression, immobilization, or high blood viscosity from leukocytosis, or erythrocytosis; and 3. treatment factors such as insertion of central venous catheter and chemotherapy leading to blood vessel injury[11]. These three important factors are compatible with Virchow's triad described as the causes of VTE[19].

VTE is a multifactorial disease. The risk of VTE increases with a higher number of individual risk factors. Some risk factors are specific to cancer disease and treatment while the others are well-known general risk factors for developing VTE. However, VTE is a preventable disease. Many recent practice guidelines suggested VTE prophylaxis with anticoagulant drugs in hospitalized cancer patients who are at risk for venous thrombotic complications[20-22].

Although there are many studies focusing on VTE in lymphoma patients, studies on VTE complications in Thai lymphoma patients are scarce. Moreover, the incidence of VTE in Thai lymphoma patients, particularly in hospitalized patients, has not been well elucidated. Therefore, the aim of this study was to identify the incidence and risk factors for VTE in Thai hospitalized lymphoma patients who are at high risk enough to receive VTE prophylaxis.

2. MATERIALS AND METHODS

This observational study was conducted as retrospective and prospective cohort study concurrently. Newly diagnosed or relapsed lymphoma patients aged at least 18 years, and admitted for chemotherapy in the medical wards of King Chulalongkorn Memorial Hospital, a university-affiliated tertiary medical center, were included. In the retrospective cohort, lymphoma patients admitted during January 1, 2007 to December 31, 2011 were identified by the International Statistical Classification of Diseases and Related Health Problems, 10th Revision Thai Modification (ICD-10-TM) codes. In the prospective cohort, lymphoma patients admitted during July 1, to December 31, 2012 were enrolled and gave written informed consent. All patients were followed up for 90 days after admission. This study was approved by the Institutional Review Board of the Faculty of Dentistry and Faculty of Pharmacy, Mahidol University, and the Faculty of Medicine, Chulalongkorn University.

Patients were excluded from the study if they had ongoing treatment with anticoagulants, VTE before entering the study, diagnosed VTE on the first date of admission, symptoms of VTE before admission and diagnosis of VTE was confirmed later, or refused to give written informed consent. Patient characteristics and risk factors were reviewed from medical records and documented in validated case record forms. In addition, patients in the prospective cohort were interviewed regarding their predisposing factors for VTE at wards and symptoms of VTE at day 90 or later by telephone.

Suspected DVT is a clinical symptom of unilateral calf swelling or pain with unknown cause. Suspected PE is either or combined clinical symptoms of unexplained dyspnea, pleuritic chest pain, or hemoptysis including sign of unexplained hypoxemia. Suspected DVT or PE was recorded if a treating physician planned further investigation or started treatment with anticoagulants.

The diagnosis of VTE was confirmed by a treating physician or radiological imaging studies that were Doppler ultrasonography, computed tomography, venography, or magnetic resonance imaging for diagnosis of DVT, and ventilation/perfusion lung scan, computed tomographic angiography, magnetic resonance imaging, or autopsy for diagnosis of PE.

The sample size in the retrospective cohort was determined from the proportion observed in the previous study of VTE in Japanese lymphoma patients[17]. A total sample of 433 patients was calculated at an alpha value of 0.05 with two-sided test, margin of error in estimating proportion of 0.3, and 20% drop out. The number of eligible lymphoma patients admitted during 6 consecutive months from July 1, to December 31, 2012 was the sample size in the prospective cohort. Patients who were followed for less than 83 days after admission, and who had unconfirmed VTE results were not included for analysis.

Demographic characteristics were presented by number of patients with percentage, mean ± standard deviation (SD), or median. Differences in continuous variables were compared by Student's t-test or Mann-Whitney U test. Risk factors for VTE were presented as relative risk (RR) with 95% confidence interval (CI) for categorical variables and *p*-values from Chi square test or Fisher's exact test. Statistic was tested at a two-sided alpha value of 0.05. The factors with *p*-values less than 0.05 from univariate analysis were selected for a multivariate analysis using a binary logistic regression model. A forward stepwise method was used for selecting the variables into the model. All data analyses were computed using SPSS version 16 (SPSS Inc., Chicago, Illinois, USA).

3. RESULTS

There were 513 eligible patients. Forty-four patients were excluded because of loss to follow-up. A total of 469 patients were included in this study, of which 422 patients were in the retrospective cohort and 47 patients were in the prospective cohort. Baseline characteristics were shown in Table 1. The mean age was 54 ± 15.6 years (range 18 – 89 years). The median length of stay was 7 days (range 1 – 182 days). Obese patients were not common in this study. The mean body mass index (BMI) was 21.9 ± 4.18 kg/m^2. Acute infection (35%), anemia (34.7%), and best rest ≥ 3 days (23.9%) were the three most frequent problems during admission. The majority of patients were newly diagnosed lymphoma (81.9%). The remaining was relapses. There were Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL) patients of 7.7% and 92.3%, respectively. The poor prognostic factors that were advanced disease (stage 3 – 4, 70.1%) and presence of B symptoms at diagnosis (53.9%) were common. Doxorubicin-based regimen (65.7%) was the major chemotherapy in this study. Almost 80% of patients were prescribed granulocyte colony-stimulating factor (G-CSF) agents after completion of each cycle of chemotherapy.

Table 1. Baseline characteristics of study patients (n= 469)

Characteristics	Number (%) or mean ± SD
Male gender	251 (53.5)
Age ≥ 60 years	170 (36.2)
Length of stay (days) (median, range)	7 (1 – 182)
Body mass index (kg/m^2) (n = 465)	21.9 ± 4.18

Table 1. Baseline characteristics of study patients (contd.)

Characteristics	Overall study (n = 469) Number (%) or mean ± SD
Problems during admission*	
No problems	183 (39)
Acute infection	164 (35)
Anemia	163 (34.7)
Bed rest ≥ 3 days	112 (23.9)
Respiratory failure	36 (7.7)
Paraparesis (grade 0 – 3)	12 (2.6)
Monoparesis (grade 0 – 3)	6 (1.3)
Congestive heart failure (FC III or IV)	3 (0.6)
Other problems	172 (36.7)
History of VTE	3 (0.6)
Recent major surgery (≤ 1 month) (n = 467)	13 (2.8)
Bedridden state	28 (6)
Varicose veins	5 (1.1)
Hormonal use	4 (0.8)
New diagnosis	384 (81.9)
Hodgkin's lymphoma	36 (7.7)
Non-Hodgkin's lymphoma	433 (92.3)
B-cell type	368 (85)
T-cell type	65 (15)
ECOG Performance status 2 – 4	202 (43.1)
Stage 3 – 4 (staging, n = 438)	307 (70.1)
Presence of bulky disease (n = 468)	121 (25.6)
Presence of B symptoms	253 (53.9)
Presence of venous compression (n = 463)	62 (13.4)
Doxorubicin-based chemotherapy regimen	308 (65.7)
Chemotherapy and radiation	10 (2.1)
Not response to the treatment (evaluated = 461)	141 (30.6)
Previous chemotherapy or radiation (≤ 6 months)	69 (14.7)
G-CSF use	374 (79.7)
Central venous catheter use	97 (20.7)
Hemoglobin (g/dL) (n = 468)	11.0 ± 2.22
Platelet (x 10^9/L) (n = 468)	251 ± 144
White blood count (x 10^9/L) (n = 468)	9.9 ± 12.08
Neutrophils (x 10^9/L) (n = 464)	6.29 ± 5.32
Lymphocytes (x 10^9/L) (n = 462)	2.61 ± 9.88
Monocytes (x 10^9/L) (n = 460)	0.569 ± 0.799
Eosinophils (x 10^9/L) (n = 453)	0.174 ± 0.378
Basophils (x 10^9/L) (n = 445)	0.038 ± 0.064

*2 - 3 problems = 113 patients, 4 - 5 problems = 57 patients, > 5 problems = 5 patients
SD: standard deviation, FC: functional class, VTE: venous thromboembolism, ECOG: Eastern Cooperative Oncology Group, G-CSF: granulocyte colony-stimulating factor agent

Nineteen patients had VTE events including 15 DVTs and 4 PEs, of which 9 events were asymptomatic. Two NHL patients in the retrospective cohort had unconfirmed VTE, and then were excluded for analysis. The incidence of VTE in the retrospective cohort was lower than that in the prospective cohort but the difference was not statistically significant (3.6%, 15/420 and 8.5%, 4/47, p=0.113). In the retrospective cohort, there were 388 NHL patients and 34 HL patients. VTE events occurred in 3.4% (13/386) of NHL compared with 5.9% (2/34) of HL patients (p=0.347). In the prospective cohort, all 4 VTEs were in NHL patients. Fifty-three patients (10.7%, 53/469) found death in this study, and most died from lymphoma disease. No patients died from VTE.

As shown in Table 2, lower extremities including intra-abdomen and lower extremity (36.8%) were common sites of VTE. One patient (5.3%) had superior vena cava (SVC) thrombosis. Six DVTs (31.6%) including SVC thrombosis were attributed to tumor mass compression. Five patients (26.3%) had upper extremity thrombosis, and four of them had central venous catheter (CVC) placement. In addition, 3 out of 4 patients had CVC-related thrombosis.

Table 2. Sites of venous thromboembolism (n = 19)

Sites	Number (%)
Neck	1 (5.3)
Upper extremities	5 (26.3)
Left	2
Right	2
Both	1
Superior vena cava (SVC)	1 (5.3)
Intra-abdomen	1 (5.3)
Lower extremities	6 (31.6)
Left	3
Right	2
Both	1
Intra-abdomen & lower extremity	1 (5.3)
Lung	4 (21.1)

The median time for VTE events after admission was 12 days (range 3 – 86 days). Out of 19 VTE patients, 9 patients (47.4%) had VTE before starting chemotherapy. The others developed VTE during the first three cycles of chemotherapy which accounted for 0.9% (4/431), 1% (4/386), and 0.6% (2/352), respectively (Figure 1).

According to univariate analysis, significant risk factors for VTE in lymphoma were shown in Table 3. The independent factors were subsequently put in a multivariate analysis using a forward stepwise method. However, three risk factors from univariate analysis including presence of venous compression, not response to the treatment, and G-CSF use were not analyzed. Because the presence of venous compression was determined only in cases undergoing imaging studies for VTE and not in all patients, this could be a bias. A routine evaluation of response to chemotherapy was usually done after 4th to 6th cycle of chemotherapy, but VTE events in this study generally occurred before those cycles. Finally, approximately 50% of VTE patients had venous thrombosis before using G-CSF agents. Therefore, these 3 factors were considered as unreasonable predictors for VTE in this study.

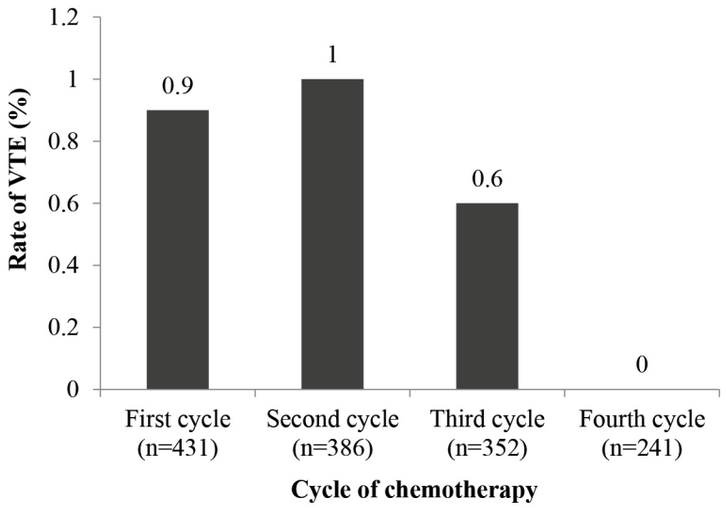

Figure 1. Venous thromboembolism rates according to cycle of chemotherapy

Table 3. Significant risk factors for venous thromboembolism by univariate analysis

Risk factors	VTE	Non-VTE	RR (95% CI)	*p*-value
Length of stay (days)	16 (4 – 68)	6 (1 – 182)	-	< 0.001*
Body mass index (kg/m^2)	19.8 ± 3.91	22.2 ± 4.11	-	0.018**
Acute infection	52.6% (10/19)	29.5% (119/404)	2.53 (1.05 – 6.08)	0.032
Bed rest ≥ 3 days	52.6% (10/19)	18.6% (75/404)	4.42 (1.85 – 10.53)	0.001
Monoparesis (grade 0 – 3)	10.5% (2/19)	1% (4/404)	8.18 (2.40 – 27.80)	0.026
Bedridden state	21.1% (4/19)	3.5% (14/404)	6.00 (2.21 – 16.26)	0.006
ECOG Performance status 2 – 4	73.7% (14/19)	37.6% (152/404)	4.33 (1.59 – 11.81)	0.004
Presence of venous compression	52.6% (10/19)	10.8% (43/399)	7.65 (3.26 –17.96)	< 0.001
Not response to the treatment	61.1% (11/18)	22.1% (88/398)	5.03 (2.00 –12.63)	0.001
G-CSF use	42.1% (8/19)	79.7% (322/404)	0.20 (0.08 – 0.49)	0.001
Lymphocytes (x 10^9/L)	0.76 ± 0.57	2.71 ± 10.52	-	< 0.001*
Eosinophils (x 10^9/L)	0.042 ± 0.076	0.179 ± 0.362	-	0.007*

The numbers in parentheses after percentage for VTE group were VTE patients who had the risk factor/all VTE patients, and that for Non-VTE group were Non-VTE patients who had the risk factor/all Non-VTE patients.
*Mann-Whitney U test, **Student's t-test
95% CI: 95% confidence interval, BMI: body mass index, ECOG: Eastern Cooperative Oncology Group Performance status, G-CSF: granulocyte colony-stimulating factor agent, RR: relative risk

Upon a multivariate analysis, the risk factors significantly associated with VTE were monoparesis (grade 0 – 3) and bedridden state with odds ratios of 15.54 (95% CI 2.59 – 93.28, p=0.003) and 7.17 (95% CI 1.80 – 28.53, p=0.005). Because one out of two patients with monoparesis had both upper extremities thrombosis despite weakness at the left lower extremity, monoparesis also was not the reasonable risk factor for predicting VTE and then was excluded from the logistic regression model. Consequently, only the bedridden state remained statistical significance with the adjusted odds ratio of 6.21 (95% CI 1.59 – 24.31, p=0.009).

4. DISCUSSION

Lymphoma has been well-recognized as a high risk group of cancer for VTE. The incidence of VTE in lymphoma varied in several studies including Asian studies. Because of more complete data records by prospective gathering, lower number of lost follow-up patients, and increased awareness of VTE in group of treating physicians at wards, the incidence of VTE in the prospective cohort was higher than that in the retrospective cohort. As a result, the incidence of VTE from the prospective cohort is likely more valid and is the representative for this study. However, a larger prospective cohort is needed for confirmation. In this study, only inpatients were included. They generally had more aggressive disease and the majority of lymphoma patients in our center received chemotherapy as outpatients. The previous studies consisted of inpatients, outpatients, or both.

According to the prospective cohort study, the incidence of VTE in this study was comparable to western studies that reported high incidence of VTE in lymphoma patients ranging from 6.4% to 17.1%[15,16,18,23]. As compared with other Asian studies, the reported number of VTE in lymphoma patients was similar. For example, a retrospective study of VTE in lymphoma patients at a medical school in the Northern Thailand showed the high prevalence of 9.3% during the year of 2007 and 2011[24]. In addition, a prospective study of VTE in Korean patients with newly diagnosed lymphoma demonstrated the incidence of 7.9% with the median follow-up of 21.8 months[25]. Another retrospective study of VTE in Japanese patients with newly diagnosed diffuse large B-cell lymphoma also reported the high incidence of 11%[17].

A large meta-analysis of 29 cohort studies including 18,018 lymphoma patients showed the higher incidence of thrombosis in NHL as compared to HL patients[15]. In contrast, a large retrospective study in hospitalized cancer patients reported the similar prevalence of VTE between NHL and HL subgroup[3]. Noticeably, a retrospective study in Thailand also revealed a higher frequency of thromboembolic complications in HL than in NHL patients[24]. The relatively small number of HL patients in the study may produce the higher proportion of VTE in HL. Furthermore, HL is uncommon in Thai patients as compared with NHL. In this prospective study, only 2 out of 47 patients were HL, and none of them had VTE.

The common site of VTE in this study was the lower extremities that consistent with other studies[15,17]. Venous compression either by an enlarged lymph node or a tumor mass may result in slow blood flow and subsequent blood clot formation[11,13]. The incidence of VTE related to venous compression in this study was higher than that reported in Thai lymphoma patients at another medical school[24]. Because CVC is inserted at the neck, chest, groin, or upper arm, it is considered as a local risk factor for upper extremity thrombosis[14]. Previous studies reported high frequency of CVC-related thrombosis of 13.5% to 28.6% in hematological patients[26,27]. However, recent practice guidelines do not recommend routine VTE prophylaxis for patients inserting catheters[22,28].

Previous studies described the highest risk for VTE existing during initial chemotherapy in lymphoma patients[15-18]. Indeed, approximately half of VTE patients in this study carried the risk before starting chemotherapy, and subsequently increased during the early courses of chemotherapy that was similar as observed in other studies[16,17,24]. Initial high tumor burden after receiving diagnosis caused high degree of generated thrombin formation after cell death during beginning chemotherapy could be explained for VTE occurrence in such period[11]. Moreover, hepatotoxicity from chemotherapy leading to decreased natural anticoagulant proteins, blood vessel injury due to high concentration of cytotoxic drugs also facilitate the blood clot formation during chemotherapy[12].

Bedridden state or immobilization resulting in inadequate blood circulation has been recognized as a well-known risk factor for VTE including in hematological patients[11,13,19]. Bedridden patients were the significant factor associated with VTE in this study. Previous studies also supported that immobilization was the most frequently encountered risk factor for VTE in hospitalized medical patients including cancers[6,7]. In addition, several recent guidelines have recommended VTE prophylaxis in cancer

patients who confine to bed or have reduced mobility[20,21]. Because there are no specific studies evaluated the benefit-risk ratio of thromboprophylaxis in hospitalized medical cancer patients. Moreover, assessment for VTE and prophylaxis of VTE in these patients are not routinely practice in our center. This result then will help to select a group of patients who would receive benefit and decrease unnecessary risk of bleeding from thromboprophylaxis.

A limitation of this study was the restricted time for conducting the study which results in short duration for follow-up. Some patients might have VTE after the 90-day follow-up period. In addition, there was the small number of participants in the prospective cohort to compare with the retrospective cohort. Besides, this study was conducted in a single medical hospital that may not be representative for all Thai lymphoma patients. Consequently, a large prospective cohort study with longer duration for VTE follow-up in other sites is required for further confirmation.

5. CONCLUSION

The incidence of VTE in Thai hospitalized lymphoma patients admitted for chemotherapy is high, especially during the initial courses of treatment. VTE prophylaxis should be considered during the first three cycles of chemotherapy in bedridden lymphoma patients.

6. ACKNOWLEDGEMENTS

This study was supported by the Graduate Studies Grant, Faculty of Pharmacy, Mahidol University. We are grateful to participating patients for cooperation, to treating physicians and nurses for their help. We are thankful to Dr. Wichai Prayoonwiwat and Dr. Nutthada Areepium for comments and suggestions from content validity test of case record forms used in this study.

REFERENCES

1. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005;293(6):715-22.
2. Angchaisuksiri P, Aticharttakarn V, Aryurachai K, Archararit N, Rachakom B, Atamasirikul K, et al. Risk factors of venous thromboembolism in Thai patients. Int J Hematol. 2007; 86(5):397-402.
3. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer. 2007;110(10):2339-46.
4. Stein PD, Beemath A, Meyers FA, Skaf E, Sanchez J, Olson RE. Incidence of venous thromboembolism in patients hospitalized with cancer. Am J Med. 2006;119(1):60-8.
5. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood. 2013; 122(10):1712-23.
6. Abdel-Razeq HN, Hijjawi SB, Jallad SG, Ababneh BA. Venous thromboembolism risk stratification in medically-ill hospitalized cancer patients. A comprehensive cancer center experience. J Thromb Thrombolysis. 2010;30(3):286-93.
7. Aniwan S, Rojnuckarin P. High incidence of symptomatic venous thromboembolism in Thai hospitalized medical patients without thromboprophylaxis. Blood Coagul Fibrinolysis. 2010;21(4):334-8.
8. Angchaisuksiri P. Venous thromboembolism in Asia--an unrecognised and under-treated problem? Thromb Haemost. 2011;106(4): 585-90.
9. Francis CW. Prevention of venous thromboembolism in hospitalized patients with cancer. J Clin Oncol. 2009;27(29):4874-80.
10. Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. J Clin Oncol. 2009;27(29): 4839-47.
11. Castelli R, Ferrari B, Cortelezzi A, Guariglia A. Thromboembolic complications in malignant haematological disorders. Curr Vasc Pharmacol. 2010;8(4):482-94.
12. Falanga A, Marchetti M. Venous thromboembolism in the hematologic malignancies. J Clin Oncol. 2009;27(29):4848-57.
13. Wun T, White RH. Venous thromboembolism in patients with acute leukemia, lymphoma,

and multiple myeloma. Thromb Res. 2010; 125(Suppl 2):S96-102.
14. Falanga A, Russo L. Epidemiology, risk and outcomes of venous thromboembolism in cancer. Hämostaseologie. 2012;32(2): 115-25.
15. Caruso V, Di Castelnuovo A, Meschengieser S, Lazzari MA, de Gaetano G, Storti S, et al. Thrombotic complications in adult patients with lymphoma: a meta-analysis of 29 independent cohorts including 18 018 patients and 1149 events. Blood. 2010; 115(26):5322-8.
16. Komrokji RS, Uppal NP, Khorana AA, Lyman GH, Kaplan KL, Fisher RI, et al. Venous thromboembolism in patients with diffuse large B-cell lymphoma. Leuk Lymphoma. 2006;47(6):1029-33.
17. Yokoyama K, Murata M, Ikeda Y, Okamoto S. Incidence and risk factors for developing venous thromboembolism in Japanese with diffuse large b-cell lymphoma. Thromb Res. 2012;130(1):7-11.
18. Zhou X, Teegala S, Huen A, Ji Y, Fayad L, Hagemeister FB, et al. Incidence and risk factors of venous thromboembolic events in lymphoma. Am J Med. 2010;123(10): 935-41.
19. Abad Rico JI, Llau Pitarch JV, Rocha E. Overview of venous thromboembolism. Drugs. 2010;70(Suppl 2):3-10.
20. Bang SM, Jang MJ, Kim KH, Yhim HY, Kim YK, Nam SH, et al. Prevention of venous thromboembolism, 2nd edition: Korean Society of Thrombosis and Hemostasis evidence-based clinical practice guidelines. J Korean Med Sci. 2014;29(2): 164-71.
21. Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. J Clin Oncol. 2015;33(6):654-6.
22. Mandala M, Falanga A, Roila F, Group EGW. Management of venous thromboembolism (VTE) in cancer patients: ESMO clinical practice guidelines. Ann Oncol. 2011;22(Suppl 6):vi85-92.
23. Ottinger H, Belka C, Kozole G, Engelhard M, Meusers P, Paar D, et al. Deep venous thrombosis and pulmonary artery embolism in high-grade non Hodgkin's lymphoma: incidence, causes and prognostic relevance. Eur J Haematol. 1995;54(3):186-94.
24. Siwasaranond N, Norasethada L, Tantiworawit A, Rattarittamrong E, Chai-adisaksopha C, Navwarawong W. Increased prevalence of thromboembolism events in Thai patients with lymphoma: the single center experience from Maharaj Nakorn Chiang Mai Hospital. J Hematol Transfus Med. 2013;23:33-41.
25. Park LC, Woo SY, Kim S, Jeon H, Ko YH, Kim SJ, et al. Incidence, risk factors and clinical features of venous thromboembolism in newly diagnosed lymphoma patients: results from a prospective cohort study with Asian population. Thromb Res. 2012; 130(3):e6-12.
26. Joks M, Czyz A, Poplawski D, Komarnicki M. Incidence and risk factors for central venous catheter-related thrombosis in hematological patients. Med Oncol. 2014; 31(1):772.
27. Van Rooden CJ, Rosendaal FR, Barge RM, van Oostayen JA, van der Meer FJ, Meinders AE, et al. Central venous catheter related thrombosis in haematology patients and prediction of risk by screening with Doppler-ultrasound. Br J Haematol. 2003; 123(3):507-12.
28. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2)(Suppl):e195S-226S.