Original Article

Risk Factors of Deep Vein Thrombosis in Cancer Patients

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ABSTRACT

Background: Venous thromboembolism (VTE) is a significant complication in cancer patients which was found in 4-20% of the patients. This study was aimed to evaluate risk factors of deep vein thrombosis (DVT) in cancer patients in an oncology center in Indonesia.

Methods: This was a retrospective cohort study. Data were obtained from medical records of adult cancer patients with DVT referring to Dharmais National Cancer Center in Indonesia since 2013-2016. Control group were adult cancer patients without DVT. Association of risk factors (sex, age, presence of metastasis, Khorana score, complete blood count and D-dimer level) with DVT were compared and analyzed between DVT patients and control group.

Results: A total of 129 cancer patients with DVT at Dharmais Cancer Hospital during year 2013-2016 met the inclusion criteria. Median age of the patients was 56 years old. Multivariate logistic regression analysis was performed to investigate the effect of sex, age, hypertension, diabetes, chemotherapeutic agents, hemoglobin level, leukocyte counts and D-dimer level to the occurrence of DVT in cancer patients. Hypertension (OR 16.7, P<0.001), chemotherapy (OR 5.0, P=0.012), D-dimer level (OR 1.00, P=0.030) and leukocyte counts (OR 1.00, P=0.017) were significant risk factors to have contribution to the occurrence of DVT in cancer patients.

Conclusion: Hypertension, history of chemotherapy, leukocytosis, and D-dimer level were significant risk factors for DVT in cancer patients.

Introduction

VTE and arterial thrombosis are among major complications in cancer patients which have been associated with 4-20% of the patients.[1-5] VTE could occur as deep vein thrombosis (DVT) or Pulmonary Embolism (PE); meanwhile arterial thrombosis includes stroke and myocardial infarction. Cancer is the main independent risk factor for the occurrence of VTE.[1-3] Prothrombotic state due to alteration in the hemostatic-coagulation system, deceleration of blood flow, endothelial dysfunction, vascular inflammation, and thrombocyte activation are main detrimental factors in the development of VTE.[1-3,5]

Although the association of cancer and thrombosis has been identified since the first report of Trousseau (1865), it has drawn the attention of the clinicians for the last 10-20 years.[6] Thromboembolism has been reported as the main cause of morbidity and mortality in cancer patients.[7] Mortality in cancer patients admitted to the hospital with DVT is almost two-folds compared to those without DVT.[7] Incidence of fatal pulmonary embolism is reported to be high in the first 30 days following occurrence of VTE in patients diagnosed with malignancy.[8] Furthermore, given the stage of the tumor and treatment regiment, cancer patients with DVT have shorter survival than those without DVT.[5]

Data on the incidence of VTE in cancer patients and associated risk factors in Indonesia is limited. Although increased in patients with cancer, the risk of VTE is highly varied among patients, even in the same patient at different timepoints. Recent developments and increased

understanding of pathophysiologic mechanisms in development of VTE in cancer resulted in a classification scheme for VTE into 4 categories; patient-related, therapy-related, cancer-related, and biomarker-related.[9-12]

Various risk factor stratification tools have been developed for identifying high risk groups for developing DVT as the pre-requirement of thromboprophylaxis administration.[13] One of these validated measures is the scoring model proposed by Khorana et al.; known as Khorana score, which was intended to identify the cancer patient with high risk features for VTE based on the presence of 5 variables (cancer location, platelet number, hemoglobin level, leukocyte count, and body mass index).[14]

This study was aimed to investigate the characteristics of patients with DVT, which is the common type of VTE in cancer patients and compare it with those in other countries.

Materials and Methods

This was a retrospective case-control study. Data were obtained from the medical record of cancer patients admitted to Dharmais National Cancer Center in Indonesia during 2013-2016. The inclusion criteria were adult patients (>18 years old) with cancer and DVT who had no history of cancer treatment in any other hospital. Diagnosis of DVT was confirmed by doppler ultrasonography examination. Control group included adult cancer patients (>18 years old) without DVT or any other VTE event.

Demographic, clinical, and laboratory characteristics were collected including: sex, age, type of malignancy, presence of metastasis, complete blood counts, D-dimer levels, and presence of comorbidities such as hypertension and diabetes mellitus. DVT was confirmed by doppler ultrasonography examination. Hypertension was defined as systolic and diastolic blood pressure persistently measured at more than 140 and 90 mmHg on minimum of two examinations, respectively. Measurement of D-dimer was done using STAGO ® latex immunoassay. Cancer type, pre-chemotherapy leukocyte and platelet count, hemoglobin level and body mass index are variables assessed in Khorana score.[13,14]

Univariate and multivariate logistic regression analyses were used to determine the odds ratio (OR) and 95% confidence interval for DVT occurrence. Variable with

Table 1: Characteristics of subjects

Characteristic	DVT (n=129)	No DVT (n=121)
Sex		
Male	33 (25.6)	47 (38.8)
Female	96 (74.4)	74 (61.2)
Age (years) [median]	53 (20 - 80)	60 (23 - 80)
Primary cancer type		
Breast cancer	31 (24.0)	34 (28.1)
Lung cancer	13 (10.1)	21 (17.4)
Cervical cancer	33 (25.6)	12 (9.9)
Hematological cancer	13 (10.1)	12 (9.9)
Prostatic cancer	6 (4.7)	4 (3.3)
Intestinal cancer	6 (4.7)	18 (14.9)
Ovarian cancer	17 (13.2)	3 (2.5)
Other cancer	10 (7.8)	17 (14.0)
Metastasis (n=247)		
Positive	50 (38.8)	45 (37.2)
Negative	79 (61.2)	73 (60.3)
Comorbidities:		
Hypertension		
Yes	39 (30.2)	23 (19.0)
No	90 (69.8)	98 (81.0)
Diabetes mellitus		
Yes	9 (7.0)	17 (14.0)
No	120 (93.0)	104 (86.0)
Khorana score		
0-2	93 (72.1)	107 (88.4)
≥3	36 (27.9)	14 (11.6)
History of chemotherapy		
Yes	46 (35.7)	33 (27.3)
No	83 (64.3)	88 (72.7)
Hemoglobin (g/dL) [mean]	10.7 (SD 2.0)	11.7 (SD 1.9)
D-dimer (g/dL) [mean]	4236.3 (SD 5491.4)	1,851.4 (SD 2098.1)
Leukocyte (/μL) [mean]	11.6 (SD 11.3) x 10^3	10.0 (SD 15.8) x 10^3
Thrombocyte (/μL) [mean]	327.4 (SD 11.3) x 10^3	314.1 (SD 135.0) x 10^3

statistical significance level of P<0.25 in univariate analysis was included in the following model of multivariate analysis. Variables with P<0.05 in multivariate analysis were considered significant. These variables included sex, age, metastasis, Khorana score, hemoglobin, leukocyte, platelet, and D-dimer levels. Statistical analyses were performed using STATA version 12.

Results

A total of 129 patients with cancer treated at Dharmais Cancer Hospital during years 2013-2016 were identified to have DVT. There were also 121 cancer patients in control group. All types of cancers; solid tumors (breast, lung, cervix, ovary, colorectal, and prostate) and hematological malignancies (leukemia, lymphoma, multiple myeloma) were included. Median age of the case and control group was 56 (SD 12.1) years. Median age in subjects with DVT was 53 (SD 11.4) years, while in control group was 60 (SD 12.7) years. 96 subjects (74.4%) in DVT group were female. The most common cancers associated with VTE were cervix (25.6%) followed by breast cancer (24.0%). 50 patients with DVT (38.8%) showed evidence of metastasis. 39 (30.2%) subjects in DVT group had hypertension and 9 subjects (7.0%) were affected by diabetes mellitus. Table 1 shows characteristics of subjects in both groups.

Table 2 shows univariate analysis between risk factors for DVT; it was found that female gender (independent of cancer type) was significantly associated with occurrence of DVT in cancer patients (OR=1.776. P=0.037). Subjects with hypertension were also at increased risk of DVT (P=0.009, OR=2.211). Furthermore, age (P=0.022, OR= 0.975), Khorana score (P<0.001, OR=1.511), hemoglobin (P=0.001, OR=0.798) and D-dimer levels (P=0.001, OR=1.000183) were also significantly associated with increased risk of DVT in cancer patients.

Multivariate logistic regression analysis was performed to investigate the effect of sex, age, hypertension, diabetes mellitus, chemotherapy, hemoglobin level, leukocyte count, and D-dimer level to the occurrence of DVT in cancer patients (Table 3). Hypertension (OR 16.7, P<0.001), chemotherapy (OR 5.0, P=0.012), D-dimer level (OR 1.00, P=0.030) and leukocyte count (OR 1.00, P=0.017) were the significant risk factors to the development of DVT.

Discussion

Multivariate analysis showed that sex was not a statistically significant risk factor in occurrence of DVT in cancer patients. Faiz et al. found that there was no significant difference in occurrence of DVT between male and female subjects.[15] Another study by Chew et al. also found that gender was not a significant risk factor for DVT in multivariate analysis.[16] However, different findings were found by Silverstein et al. that risk of DVT was higher among male subjects with cancer who were older than 50 years of age.[17]

In multivariate analysis, age was found to be statistically insignificant. In a study performed in hospitalized patients with cancer, older age (≥65 years) was associated with the higher risk of VTE.[18] Likewise, in surgical settings, VTE was more common in patients above 60 years of age.[19,20]

Risk factors of cardiovascular disease such as: smoking, obesity, hypertension, dyslipidemia, and diabetes were commonly observed in cancer patients. Several studies showed conflicting results regarding the impact of various comorbidities on occurrence of DVT. Metabolic syndrome has shown to increase the risk of thromboembolism in cancer patients.[21,22] However, the contradicting results have also found in which smoking, hypertension, dyslipidemia, and diabetes do not increase the risk of DVT independently.[23,24] In our analysis there was no association between diabetes and VTE. It was discovered that diabetes, hypertension, high-density lipoprotein,

Table 2: Univariate analysis

Variables	OR	95% CI	P value
Male	1.776	1.034-3.051	0.037
Age (years)	0.975	0.955-0.996	0.022
Khorana Score	1.511	1.216-1.877	< 0.001
History of chemotherapy	1.5	0.850-2.648	0.162
Metastasis	1.07	0.641-1.785	0.797
Comorbidities			
- Hypertension	2.211	1.217-4.018	0.009
- Diabetes mellitus	0.46	0.189-1.120	0.087
Laboratories			
- Hemoglobin	0.798	0.698-0.912	0.001
- Leukocyte	1.000018	0.9999941 - 1.000041	0.142
- Trombocyte	1.000001	0.9999991 - 1.000003	0.347
- D-dimer	1.000183	1.000072 - 1.000294	0.001

Table 3: Final model of multivariate analysis

Variabel	B	SE	OR	95% CI	P value
Hypertension	2.8	0.6	16.7	4.9-56.5	<0.001
History of chemotherapy	1.6	0.6	5.0	1.4-17.5	0.012
D-Dimer	0.0	0.0	1.0	1.0 - 1.0	0.030
Leukocyte	0.0	0.0	1.00	1.0 - 1.0	0.017

low-density lipoprotein cholesterol, and triglyceride levels were not associated with risk of VTE in a cohort of 15340 participants who were followed-up for more than 15 years.[25] However, the present study found hypertension to be significantly associated with VTE in the multivariate analysis (OR 16.7; 95%CI: 4.9-56.5). Similar results were found on the study by Zhang et al. in which hypertension was a significant risk factor for VTE in patients with lung cancer.[26] Hong et al. also found that among non-cancer patients, hypertension was an independent risk factor to the occurrence of VTE.[27] Another study by Aranzazu et al. on non-cancer patients showed different findings that hypertension did not increase risk of VTE in all age groups.[28] The triad of alteration in tumor biology, coagulation activation, and inflammation were the main pathogenetic mechanisms in development of thrombosis in malignancy.[9,29,23] Hypertension could be associated with endothelial dysfunction and inflammation, thus could increase the risk of thrombosis.[26,27]

The impact of cancer stage is not well studied in cancer patients. A study by Tagalakis et al. in patients with non-small cell lung cancer showed that DVT was more common in more advanced stages of the cancer.[30] In our study, metastasis was not significantly associated with increased risk of DVT. This was different with the results of the study by Tagalakis et al. It could be explained because our study included all type of cancers (solid tumors and hematological malignancies). Gade et al. has also reported different risks for VTE among various cancer types.[31]

This study showed a significant impact of chemotherapy on the occurrence of DVT in cancer patients (OR 5.0; 95%CI: 1.4-17.5). Our results were similar to the previous study by Otten et al. which found that 7.3% of patients had VTE during or within 3 months after chemotherapy, and the incidence of VTE was specifically high in 39 patients treated with a combination of fluorouracil and leucovorin calcium for colorectal cancer.[32] Chemotherapeutic agents are capable of alterations in coagulation factors and anti-coagulant proteins and also changes in endothelial cells after exposure to the cytotoxic agents.[13,33] Other therapy related factors are: history of surgery, hospital admission, hormonal therapy, central venous catheterization, and multiple transfusions.[14,34,19]

In this study, D-dimer level was associated significantly to the risk of DVT occurrence when multivariate analysis was considered. D-dimer is the degradation product of cross-linked fibrin which indicates the activation of coagulation system and fibrinolysis. D-dimer level is also elevated in malignant conditions. There are numerous studies that have investigated the association between D-dimer and DVT in malignancies.[35] Ay et al. reported that cancer patienst with elevated D-dimer levels have a three times higher risk of developing VTE.[36] Meanwhile, initial D-dimer levels in cancer patients prior to chemotherapy were significantly associated with the risk of VTE.[37] We also found that mean D-dimer level in group of patients with cancer and DVT was higher compared to the control group. Several other biomarkers that might predict occurrence of VTE in cancer patients

has been proposed by Vienna Cancer and Thrombosis Study (CATS) and include: SP-selectin, factor-VIII, prothrombin, fragment F1+ F2, peak thrombin generation and highly elevated thrombocyte.[38-42]

Leukocytosis was another biomarker found to be significantly related to DVT in this study. Leukocytosis is known to be involved in the development of atherosclerosis and coronary heart disease, and could be a predictor of cardiovascular event.[43] Monocytes and neutrophils are leukocytes mainly involved in the pathogenesis of VTE.[44]

Khorana score is one of validated model to assess risk of VTE in cancer patients. Cancer type, pre-chemotherapy leukocyte and thrombocyte count, hemoglobin level and body mass index are variables assessed in Khorana score.[13,14] Although our study showed a 1.5 times higher risk of DVT in cancer patients with Khorana score >3 (high risk group), this result could not be validated on the multivariate regression analysis (P=0.535). It is contradicted to the study by Vienna Cancer and Thrombosis Study (CATS), in which Ay et al. independently validated Khorana score in a group of 819 patients of various malignancies.[45] In the analysis conducted specifically according to each component of Khorana score, we found that leukocytosis was the most significant independent risk factor for DVT occurrence compared to other variables in the Khorana score.

There were several limitations in this study: 1) It included all kinds of cancers and sample size was not large enough to make a conclusive analysis, thus further studies with larger sample size are needed to investigate the authentic risk factors for specific type of cancer and to make a conclusive analysis, 2) the study specifically investigated risk factors for DVT occurrence, excluding pulmonary embolism and arterial thrombosis, 3) the duration between the time of cancer diagnosis and the event of VTE was not investigated, 4) the presence of other risk factors, either already proven or proposed, which were not investigated in this study due to the resource limitation and incomplete medical record.

Conclusion

Various efforts were performed during the last decade to improve our understanding on cancer related risk factors of VTE. Significant risk factors of DVT occurrence found in this study were hypertension, history of chemotherapy, leukocytosis, and D-dimer level. Further studies with larger sample size are needed to investigate other risk factors of DVT in different kinds of cancer patients.

Ethics Approval

This study has been reviewed and approved by Ethical Committee of Dharmais National Cancer Centre Hospital - Indonesia.

Availability of Data and Materials

The data that support the findings of this study are available from Medical Record Divison of Dharmais National Cancer Centre Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly

available. Data are however available from the authors upon reasonable request and with permission of Medical Record Divison of Dharmais National Cancer Centre Hospital.

Conflict of Interest: None declared.

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