Clinical and Applied Thrombosis/Hemostasis
Volume 27: 1-5

DOI: 10.1177/10760296211037923
journals.sagepub.com/home/cat
SAGE

Risk Factors of Thromboembolism in Lymphoma Patients Undergoing Chemotherapy and its Clinical Significance

Xiao Li, MM[1], Shu-Ling Hou, MM[2], Xi Li, MM[2], Li Li, MM[2], Ke Lian, MM[2], Ju-Ya Cui, MM[2], Gang-Gang Wang, MM[2], and Tao Yang, PhD[2]

Abstract

This study investigated the risk factors of thromboembolism (TE) in lymphoma patients undergoing chemotherapy and its clinical significance. A total of 304 lymphoma patients who received chemotherapy from January 2012 to July 2019 were retrospectively analyzed, including 111 patients with and 193 patients without TE. The clinical characteristics and related laboratory test results were compared between the 2 groups using univariate analysis, while the risk factors for TE in lymphoma patients undergoing chemotherapy were analyzed using multivariate logistic regression analysis. Univariate analysis revealed an increase in the risk of TE among lymphoma patients with chemotherapy in the following categories: female patients, patients with body mass index <18.5 or > 24, patients aged ≥60 years, those with platelet abnormality before chemotherapy, single hospital-stay patients, and Ann Arbor stage III/IV patients. Multivariate logistic regression analysis revealed that for platelet count abnormality before chemotherapy, Ann Arbor stage III/IV and female patients represented independent risk factors for TE among lymphoma patients after chemotherapy ($P < .05$). For lymphoma patients treated with chemotherapy, the risk of TE occurring in women, patients with platelet abnormalities before chemotherapy, and patients at Ann Arbor stage III/IV was significantly higher compared with other patients. For these patients, we recommend prophylactic anticoagulant therapy.

Keywords

lymphoma, chemotherapy, thromboembolism, risk factor

Date received: 3 March 2021; revised: 7 July 2021; accepted: 20 July 2021.

Introduction

Thromboembolism (TE) is a major complication among cancer patients. Its incidence rate in cancer patients is approximately 5 times higher than among the general population. Previous studies revealed the incidence of TE in patients with hematological malignancies to be similar to or even higher than in patients with solid cancers.[1–4] Approximately 20% of cancer patients develop venous TE (VTE) during the course of the disease. Autopsy confirms VTE in up to half of cancer patients, leading to the conclusion that VTE is a seriously underestimated cancer complication.[5–7]

Currently, lymphoma is one of the fastest-growing malignant tumors in the world, with an average 4% annual increase in incidence. In recent years, the incidence rate of malignant lymphoma has increased rapidly in China. The incidence rate of non-Hodgkin lymphoma is the highest in the case of lymphoma at an incidence rate of approximately 6 to 7 of 0.1 million, while for Hodgkin lymphoma it is 2 to 3 of 0.1 million.[8] The incidence of TE in patients with hematological malignancies ranges from 1.5% to 59.5% in lymphoma patients.[9,10]

Among the complications of lymphoma, TE is the most prevalent. Therefore, to prevent and intervene in the occurrence of TE among lymphoma patients, analysis of its risk factors has become an important task. The current paper presents a clinical case-control study conducted to analyze the possible risk factors for TE in lymphoma patients undergoing chemotherapy. The

[1] Department of Thoracic Oncology, Linfen Central Hospital, Linfen, China
[2] Bethune Hospital Affiliated to Shanxi Medical University, Shanxi Bethune Hospital, Taiyuan, China

Corresponding Author:
Shu-Ling Hou, Department of Lymphatic Oncology, Shanxi Bethune Hospital, Taiyuan 030000, China.
Email: shuling_drhou@163.com

aim of doing so was to provide a basis for clinical prevention, intervention, and treatment, reduce the occurrence of TE, and further improve the survival and quality of life of patients.

Data and Methods

General Information

From January 2012 to July 2019, 304 patients with lymphoma who had been diagnosed by pathology and received chemotherapy in Shanxi Bethune Hospital (former Shanxi Hospital), China, were selected (185 male and 119 female patients). The average age of these patients was 50.4 years old (22-89 years old). Inclusion criteria were as follows. A diagnosis was confirmed by histopathology, and the diagnostic criteria were based on the World Health Organization (WHO) classification of hematopoiesis and lymphoid tissue tumors (WHO 2016). Patients and their families provided signed informed consent for participating in the study. No other organic lesions were involved and clinical data were complete. Exclusion criteria included patients complicated with other infectious or hematological malignancies; patients who were unable to cooperate with the study procedures; patients with deep vein thrombosis or thrombophlebitis before chemotherapy, and other related diseases; patients with other basic diseases, such as hypertension and dyslipidemia; patients who failed to receive chemotherapy.

A total of 111 patients developed TE, including 52 cases of diffuse large B-cell lymphoma, 16 cases of t-lymphoblastoma, 1 case of angioimmunoblastic lymphoma, 12 cases of mantle cell lymphoma, 7 cases of marginal zone B-cell lymphoma, 12 cases of NK/T-cell lymphoma, 3 cases of follicular type lymphoma, 3 cases of intestinal disease-related T-cell type lymphoma, 1 case of plasma cell lymphoma, and 4 cases of classical Hodgkin lymphoma. All patients were treated with the recommended chemotherapy regimen. This study meets the ethical requirements of the Declaration of Helsinki; all patients' personal privacy information has been deleted from the research database.

Diagnosis of Thromboembolism

Cases of venous and arterial TE were analyzed in this study. An objective diagnosis of TE was made according to radiological examination (venous ultrasound of both lower limbs, enhanced chest computed tomography [CT] scan, magnetic resonance imaging [MRI], central nervous system thrombosis, or angiography [arterial thrombosis], clinical examination, and laboratory evaluation).

A total of 111 TE patients were diagnosed, 86 of whom were diagnosed by ultrasonography, 17 by CT, 6 by MRI, and 2 patients by angiography. Among the 111 patients with thrombus, 67 patients showed TE symptoms and the rest 44 patients did not. All patients included in the study were examined by imaging after chemotherapy to determine whether TE had occurred after the chemotherapy. The diagnoses were reviewed by a final diagnosis committee comprising physicians and radiologists.

Methods and Data Collection

The general information, diagnosis, and treatment of patients were collected, and the risk factors of TE were analyzed. The specific data collected included patient age, gender, disease type, Ann Arbor stage, thrombosis and location, blood cell count before chemotherapy, coagulation series index, body mass index (BMI), and single hospitalization days. The type of disease was determined by pathology. The disease was classified according to the Ann Arbor staging standard. Meanwhile, color Doppler ultrasound of both lower limbs, heart color Doppler ultrasound, and head CT was conducted to determine whether TE had occurred during single hospitalization, and if so, its location. Before chemotherapy, the number of blood cells including white blood cells, hemoglobin, and platelet count were detected. Blood tests were also performed during cycles 2, 4, 6, and 8 of chemotherapy.

Coagulation parameters included prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), D-dimer (DD), and plasma fibrinogen (FIB).

Statistical Analysis

Data were analyzed using SPSS 23.0 statistics software. Count data were compared using a χ^2 test. Normally distributed measurement data were compared using an independent sample *t*-test, and nonnormally distributed measurement data were compared using a corrected *t*-test. The risk factors for TE in lymphoma patients undergoing chemotherapy were analyzed using multivariate logistic regression analysis; $P < .05$ was considered statistically significant.

Results

Univariate Analysis of the Risk Factors for TE in Lymphoma Patients Undergoing Chemotherapy

Univariate analysis revealed that gender, BMI, age, platelet count before chemotherapy, single hospital stay, and Ann Arbor stage were significantly correlated with TE ($P < .05$ for all results, Table 1). Meanwhile, blood samples which were collected at the time of diagnosis of thrombosis including the white and red blood cell count, hemoglobin count, lactate dehydrogenase value, PT, APTT, TT, FIB, and DD were evaluated by independent sample *t*-test. The correlation between these factors and TE occurrence was not statistically significant ($P > .05$ for all results, Table 2).

Multivariate Analysis of the Risk Factors for TE in Lymphoma Patients Undergoing Chemotherapy

Study variables were selected based on the results of univariate analysis and the clinical significance of the influencing factors. With the occurrence of TE as the dependent variable, and gender, age, BMI group, single hospitalization >30 days, platelet count before chemotherapy, and Ann Arbor stage as the

Table 1. Single Factor Analysis of Thromboembolism and Influencing Factors ($n = 304$).

	No TE ($n = 193$)		TE ($n = 111$)			
Project	Number	Composition ratio (%)	Number	Composition ratio (%)	χ^2	P
Gender					59.29	< .001
Female	44	22.8	75	67.6		
Male	149	77.2	36	32.4		
BMI					91.90	< .001
< 18.5 or > 24	50	25.9	92	82.9		
18.5 ≤, ≤ 24	143	74.1	19	17.1		
Age					171.54	< .001
≥ 60	23	11.9	98	88.3		
< 60	170	88.1	13	11.7		
Platelets					220.02	< .001
< 125 or > 350	10	5.2	100	90.1		
125 ≤, ≤ 350	183	94.8	11	9.9		
Length of stay					11.10	.001
< 30 days	136	70.5	57	51.4		
≥ 30 days	57	29.5	54	48.6		
Stage					156.58	< .001
I	99	51.3	5	4.5		
II	70	36.3	16	14.4		
III	19	9.8	31	27.9		
IV	5	2.6	59	53.2		

Abbreviations: BMI, body mass index; TE, thromboembolism.

independent variables, multivariate logistic regression analysis was carried out (Table 3).

The logistic regression model result was $\chi^2 = 294.46$, with $P < .01$; as such, the model indicated a good fit. Abnormal platelet count was an independent risk factor for TE ($P < .05$), and the risk of TE was 63.54 times higher than for people with normal platelet values. Gender was an independent risk factor for TE ($P < .05$), where the risk of TE among women was 6.69 times higher than in men. Ann Arbor stage was also an independent risk factor for TE ($P < .05$), and the risk of TE among stages III and IV patients was 3.42 times higher than among stages I and II patients.

Discussion

The risk of venous thrombosis in hematologic malignancies patients was 10 times higher than in patients with lung cancer and gastrointestinal cancer.[11] Moreover, VTE is a common disease of TE in lymphoma patients and a major death factor.[12] The results of the present study revealed that VTE occurred in 102 of 111 patients with TE, including 10 patients with catheter-related thrombosis and 9 patients with arterial thrombosis. Based on the results of this study, for patients receiving lymphoma chemotherapy, at admission, chest CT, electrocardiograph, and ultrasound examination of both lower limbs should be routinely performed to determine whether patients have developed TE. For high-risk patients, if necessary, they can be given low-molecular-weight heparin as a means of anticoagulant therapy after evaluation of general conditions.

Many chemotherapeutic drugs are known to be associated with thrombosis, and several studies in China and other countries proposed a correlation between chemotherapy and arteriovenous thrombosis. Vascular endothelial growth factor inhibitors and vascular endothelial growth factor tyrosine kinase receptor inhibitors are associated with increased thrombosis rates.[13] A study also reported that immunosuppressive or cytotoxic chemotherapy, such as L-aspartase, thalidomide, lenalidomide, and tamoxifen increased the risk of VTE.[14] Lymphoma patients undergoing chemotherapy are typically treated, among others, with immunosuppressive or cytotoxic drugs, and vascular endothelial growth factor inhibitors, all of which increase the risk of developing TE.

In the present study, univariate analysis revealed that in lymphoma patients, platelet count prior to chemotherapy, Ann Arbor stage, and gender were independent risk factors for developing TE after chemotherapy. Among these, platelet count differed from the normal level, where the risk of TE was increased by more than 60 times. The risk of TE in women was higher than in men, and patients at Ann Arbor stages III and IV had a significantly higher risk of developing TE.

For lymphoma patients undergoing chemotherapy, abnormal platelet count was an independent risk factor for TE. The molecular mechanism of TE development remains unclear. The main reason for this is that tumor cells directly or indirectly activate platelet and coagulation pathways through the expression and release of related cytokines, for example, through tumor microparticles, tissue factor, podoplanin, and plasminogen activator inhibitor directly binding to the receptors expressed on platelets' surface, such as CLEC-2, P2Y12, and PAR1/4. Furthermore, inflammatory cytokines secreted by tumor cells, such as tumor necrosis factor α and interleukin-β, lead to platelet activation, and promote endothelial cells to form the procoagulant phenotype.[15] In addition, tumor-derived

Table 2. Independent Sample *t*-Test of Thromboembolism and Influencing Factors ($n = 304$).

Project	*T*	*SE*	Degree of freedom	Difference 95% confidence interval		*P*
				Lower limit	Upper limit	
Leukocyte	−0.41	0.24	302.00	−0.58	0.38	.683
Red blood cell	−1.09	0.10	302.00	−0.30	0.09	.279
Hemoglobin	−0.90	1.73	302.00	−4.97	1.86	.371
Lactate dehydrogenase	−1.26	3.01	302.00	−9.74	2.12	.208
PT	1.21	0.22	302.00	−0.17	0.71	.226
APTT	−0.02	0.56	301.00	−1.10	1.08	.986
TT	−1.48	0.29	297.00	−1.01	0.14	.140
FIB	0.73	0.15	301.00	−0.18	0.39	.464
DD	0.90	8.39	302.00	−9.00	24.01	.372

Abbreviations: PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; DD, D-dimer; FIB, plasma fibrinogen.

factors can promote the release of neutrophil extracellular traps (NETs) from neutrophils, which can capture and activate platelets and further cause fibrin deposition, red-blood-cell capture, and exacerbate blood clot formation. Conversely, the coagulation activity produced by NETs can further promote tumor growth.[16,17] Lymphoma patients undergoing chemotherapy are prone to moderate to severe myelosuppression, leading to a decrease in peripheral platelet count, and extremely prone to thrombocytopenia, have a risk of bleeding, and developing thrombosis.[18] Tests, such as routine blood tests, should be conducted regularly during preventive anticoagulation therapy; close attention should be paid to whether the patient has skin bleeding, gingival bleeding, hematochezia, hematemesis, or any other related condition to avoid significant and potentially life-threatening bleeding. In follow-up studies, the extent of platelet abnormalities before chemotherapy should be defined, and the risk of TE in lymphoma patients should be evaluated.

Byun et al[3] revealed that the risk of TE in women was significantly higher than in men. Additionally, the risk of TE in stage III and IV patients was significantly higher than in stage I and II patients. Komrokji et al[19] revealed stage I disease to be associated with a low risk of TE. This is consistent with the results of the current study. Considering that patients with advanced lymphoma are often associated with multiple organ failure, during chemotherapy, endothelial cell damage revealed by elevated plasma von Willebrand factor levels is considered a major contributing factor to the risk of TE.[20] In addition, a study revealed that the use of chemotherapeutic drugs increased the risk of TE in several ways. Chemotherapy can induce apoptosis of tumor cells and endothelial cells, the secretion of cytokines, the expression and activation of tissue factor, and the activation of platelets.[21,22] Blood in lymphoma chemotherapy patients was in a hypercoagulable state and, as such, patients were more prone to TE.[23] One mechanism of hypercoagulability in cancer patients is the role of anti-tumor factor (TF).[24–26] TF is a transmembrane glycoprotein that plays an important role in the coagulation pathway and is a receptor that binds to essential cofactors, factor II and activated factor VII, leading to procoagulant and fibrin formation.[27] Accordingly, a larger focus is needed on patients with advanced cancer to observe whether they indicate clinical manifestations, such as discomfort in the lower limbs, chest tightness, tightness of breath, chest pain, and disturbances in consciousness. If necessary, prophylactic anticoagulant therapy can be given to high-risk patients.

Clinically, the incidence of TE in lymphoma chemotherapy patients increases gradually. For different patients, risk assessment of TE should be performed on admission, with attention given to the risk of TE and realizing individualized treatment for different patients as the basis for prevention. Currently, a range of scales are used for assessing the risk of thrombosis among patients in China and other countries. However, these scales are not entirely suitable for the risk assessment of thrombosis in patients with hematological malignancies, particularly lymphoma.[24,28] Therefore, to improve the quality of life and prolong the survival of patients, the thrombus risk scale for lymphoma patients should be further developed to better formulate relevant prophylactic anticoagulant programs.

The current research was a single-center retrospective study. Research limitations relate to participant selection, retrospective bias, and small sample size. Multicenter, large-scale studies are needed to screen out variables with high specificity related to TE risk in lymphoma patients undergoing chemotherapy, which will help to establish and verify effective prediction scales and improve the accuracy of predictions to improve the quality of life and prolong the survival of patients.

Table 3. Logistic Regression Analysis of Factors Affecting Thrombosis.

Project	*B*	*SE*	Wald	*df*	*P*	OR	95% confidence interval of Exp(*B*)	
							Lower limit	Upper limit
Stage	1.231	0.452	7.411	1	.006	3.425	1.412	8.310
BMI	0.536	0.626	0.731	1	.392	1.709	0.501	5.832
Age	−0.148	0.899	0.027	1	.869	0.862	0.148	5.024
Platelets	4.152	0.598	48.193	1	.000	63.541	19.679	205.166
Length of stay	0.410	0.599	0.470	1	.493	1.507	0.466	4.871
Gender	1.901	0.551	11.895	1	.001	6.696	2.273	19.728

BMI, body mass index.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

ORCID iD

Shu-Ling Hou https://orcid.org/0000-0003-4641-9010

References

1. Colombo R, Gallipoli P, Castelli R. Thrombosis and hemostatic abnormalities in hematological malignancies. *Clin Lymphoma Myeloma Leuk*. 2014;14(6):441-450.
2. Falanga A, Marchetti M, Russo L. Venous thrombo-embolism in the hematologic malignancies. *Curr Opin Oncol*. 2012;24(6):702-710.
3. Byun JM, Hong J, Yoon SS, et al. Incidence and characteristics of venous thromboembolism in Asian patients with primary central nervous system lymphoma undergoing chemotherapy. *Thromb Res*. 2019;183:131-135.
4. Khorana AA, Francis CW, Culakova E, et al. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. *Cancer*. 2007;110(10):2339-2346.
5. Donnellan E, Kevane B, Bird BR, et al. Cancer and venous thromboembolic disease: from molecular mechanisms to clinical management. *Curr Oncol*. 2014;21(3):134-143.
6. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American college of chest physicians evidence-based clinical practice guidelines (8th edition). *Chest*. 2008;133(6 Suppl):381S-453S.
7. Khorana AA, Francis CW, Culakova C, et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost*. 2007;5(3):632-634.
8. Caruso V, Castelnuovo A, Meschengieser 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):5322-5328.
9. Goldschmidt N, Linetsky E, Shalom E, et al. High incidence of thromboembolism in patients with central nervous system lymphoma. *Cancer*. 2003;98(6):1239-1242.
10. Zhou X, Teegala S, Huen A, et al. Incidence and risk factors of venous thromboembolic events in lymphoma. *Am J Med*. 2010;123(10):935-941.
11. Blom JW, Doggen CJ, Osanto S, et al. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA*. 2005;293(6):715-722.
12. Levitan N, Dowlati A, Remick SC, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. *Medicine (Baltimore)*. 1999;78(5):285-291.
13. Herrmann J, Yang E, Alliescu C, et al. Vascular toxicities of cancer therapies: the old and the new—an evolving avenue. *Circulation*. 2016;133(13):1272-1289.
14. John AH. Epidemiology of venous thromboembolism. *Nat Rev Cardiol*. 2015;12(8):464-474.
15. Falanga A, Panova-Noeva M, Russo L. Procoagulant mechanisms in tumour cells. *Best Pract Res Clin Haematol*. 2009;22(1):49-60.
16. Bevilacqua MP, Pober JS, Majeau GR, et al. Recombinant tumor necrosis factor induces procoagulant activity in cultured human vascular endothelium: characterization and comparison with the actions of interleukin 1. *Proc Natl Acad Sci U S A*. 1986;83(12):4533-4537.
17. Nawroth PP, Stern DM. Endothelial cell procoagulant properties and the host response. *Semin Thromb Hemost*. 1987;13(4):391-397.
18. Kopolovic I, Lee AY, Wu C. Management and outcomes of cancer-associated venous thromboembolism in patients with concomitant thrombocytopenia: a retrospective cohort study. *Ann Hematol*. 2015;94(2):329-336.
19. Komrokji RS, Uppal NP, Khorana AA, et al. Venous thromboembolism in patients with diffuse large B-cell lymphoma. *Leuk Lymphoma*. 2006;47(6):1029-1033.
20. Nuver J, Smit AJ, van der Meer J, et al. Acute chemotherapy-induced cardiovascular changes in patients with testicular cancer. *J Clin Oncol*. 2005;23(36):9130-9137.
21. Shinagare AB, Guo M, Hatabu H, et al. Incidence of pulmonary embolism in oncologic outpatients at a tertiary cancer center. *Cancer*. 2011;117(16):3860-3866.
22. Blom JW, Vanderschoot JP, Oostindir MJ, et al. Incidence of venous thrombosis in a large cohort of 66329.cancer patients: results of a record linkage study. *J Thromb Haemost*. 2006;4(3):529-535.
23. Bick RL, Strauss JF, Frenkel EP. Thrombosis and hemorrhage in oncology patients. *Hematol Oncol Clin North Am*. 1996;10(4):875-907.
24. Lip GY, Chin BS, Blann AD. Cancer and the prothrombotic state. *Lancet Oncology*. 2002;3(1):27-34.
25. Dasmahapatra KS, Cheung NK, Spillert C, et al. An assessment of monocyte procoagulant activity in patients with solid tumors. *J Surg Res*. 1987;43(2):158-163.
26. Callander NS, Varki N, Rao LV. Immunohistochemical identification of tissue factor in solid tumors. *Cancer*. 1992;70(5):1194-1201.
27. Nemerson Y, Bach R. Tissue factor revisited. *Prog HaemostasisThromb*. 1982;6:237-261.
28. Antic D, Milic N, Nikolovski S, et al. Development and validation of multivariable predictive model for thromboembolic events in lymphoma patients. *Am J Hematol*. 2016;91(10):1014-1019.