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Incidence of Venous Thromboembolism in Patients with Non-Hodgkin Lymphoma

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Abstract

Introduction—Patients with non-Hodgkin lymphoma (NHL) have an increased risk of venous thromboembolism (VTE). Current risk-prediction models classify NHL as a single entity. We aimed to quantify the difference in VTE risk in follicular lymphoma (FL) versus diffuse large B cell lymphoma (DLBCL).

Methods—Using a prospective cohort study, we identified 2,730 patients (2,037 DLBCL; 693 FL) within the Veteran's Administration Central Cancer Registry. A competing risk model assessed the association between VTE risk and histology in the first year after NHL diagnosis. We assessed the effect of additional risk factors for VTE in NHL.

Results—In univariate analysis, DLBCL was associated with increased risk of VTE compared to FL in the first year after diagnosis; this association was no longer significant in adjusted analysis (adjusted hazard ratio (aHR) 1.52; 95% CI 0.97–2.40). Major risk factors for VTE included history of VTE before NHL diagnosis (aHR 4.73, $p < 0.0001$) and time period during chemotherapy administration (aHR 7.60, $p < 0.0001$). Additional risk factors included: stage III/IV disease ($p = 0.02$), BMI ≥ 30 ($p = 0.02$), B-symptoms ($p = 0.02$), and doxorubicin ($p = 0.04$). The cumulative incidence of VTE was highest in the period following diagnosis and decreased over time for both histologies.

Conclusion—DLBCL is associated with increased risk of VTE compared to FL. This risk is markedly attenuated when adjusting for additional risk factors. The strongest predictors for development of VTE included: time period during chemotherapy administration (especially doxorubicin) and history of VTE. This knowledge can assist clinicians in identifying NHL patients at high risk for VTE.

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Role of Each Author

K. Sanfilippo and K. Carson designed the research. K. Sanfilippo, B. Gage, S. Luo, and K. Carson performed the research. S. Luo performed the statistical analyses. K. Sanfilippo, T. Wang, B. Gage, P. Riedell analyzed the research and formulated the conclusions. All authors contributed to the writing of the manuscript.

Keywords

Non-Hodgkin Lymphoma; Venous Thromboembolism; Risk; Cancer; Thrombosis

INTRODUCTION

Venous thromboembolism (VTE) is a leading cause of death in patients with cancer[1, 2]. The American Society of Clinical Oncology (ASCO) recommends routine assessment of thrombosis risk in patients with newly diagnosed cancer and suggests use of a validated VTE risk prediction model[3, 4]. Patients with hematologic malignancies, such as non-Hodgkin lymphoma (NHL), have an increased risk of VTE[5–7]. VTE risk prediction models aggregate all NHL as a single risk cohort[4, 8, 9]; however, recent studies suggest that the rate of VTE differs based on NHL histology, with the highest rates in aggressive lymphomas, such as diffuse large B cell lymphoma (DLBCL)[10–15].

Given the apparent heterogeneity of VTE risk in NHL, using available prediction models that define NHL as a homogenous disease may over- or under-estimate VTE risk. Misclassification of risk can unnecessarily expose low-risk patients to thromboprophylaxis, or lead to failure to prescribe thromboprophylaxis in high-risk patients. Understanding VTE risk in NHL can allow for more accurate stratification of VTE risk in prediction models and facilitate identification of patients who may benefit from thromboprophylaxis [16, 17].

Here, we use a large cancer-registry to compare VTE risk between follicular lymphoma (FL), the most common indolent NHL, versus DLBCL, the most common aggressive NHL. In addition, we identify clinical and laboratory risk factors associated with VTE in NHL. To allow for identification of the period during which thromboprophylaxis would have the greatest benefit, we describe the timing of thrombosis in NHL.

METHODS

Study Cohort

We assembled a cohort of patients diagnosed between October 1, 1998 and December 31, 2009, using *International Classification of Disease-O3* (ICD-O3) codes from the Veterans Administration Central Cancer Registry (VACCR), with DLBCL (I-O3 codes 9680 or 9684) or FL (ICD-O3 codes 9690, 9691, 9695, 9698). To eliminate confounding based on treatment, we excluded patients who did not receive treatment or who received treatment regimens other than CHOP (cyclophosphamide, adriamycin, vincristine, prednisone)-like regimens. We also excluded patients with primary central nervous system DLBCL. Patients were followed from time of diagnosis until development of VTE, death, or loss to follow up; whichever came first. In the VTE analysis, we censored patients at the time of death or loss to follow up. Institutional Review Boards of the Veterans Health Administration (VHA) Saint Louis Medical Center and Washington University School of Medicine approved the study prior to chart review.

Measurements

We extracted data on sex, race, lactate dehydrogenase (LDH), hemoglobin (HGB), NHL histology, stage, B-symptoms, body mass index (BMI), medical co-morbidities, chemotherapy use, and occurrence of VTE. We identified B-symptoms (defined as the presence of fever ($> 38^{\circ}\text{C}$), drenching night sweats, or 10% loss in body weight in the 6 months preceding diagnosis) using a combination of VACCR data, structured manual review of provider clinical notes, and vital sign data. We calculated the Romano adaptation of the Charlson comorbidity index for each patient at the time of diagnosis using ICD-9 codes[18]. We identified administration of chemotherapy with CHOP or CHOP-like regimens +/- rituximab using Pharmacy Benefits Management (PBM) records. Time during chemotherapy administration was defined as PBM record of the first dose of chemotherapy prescription until plus 30 days past the last dose of chemotherapy. We identified VTE, defined as deep vein thrombosis (DVT), pulmonary embolism (PE), or both DVT and PE, by using a validated algorithm that requires an ICD-9 diagnostic code for VTE plus either anticoagulant therapy, common procedural terminology (CPT) code for placement of a vena-cava filter, or death within 30 days of ICD-9 diagnosis of VTE[19]. History of VTE could occur at any time before NHL diagnosis. To prevent false positive diagnoses caused by anticoagulant therapy for atrial fibrillation, we manually extracted charts of these patients (ICD-9 code 427.31) and reviewed the results for objective VTE testing (Doppler venous ultrasound, venography, pulmonary embolism protocol computerized tomography (CT), CT angiography, and ventilation perfusion scans).

Statistical Analyses

We compared baseline characteristics between the DLBCL and FL groups using Chi-square and Cochran-Mantel-Haenszel tests on categorical variables and the unpaired Student's t-test on continuous variables. The primary objective of the study was to determine the risk of VTE in patients with DLBCL compared to FL within one year after the diagnosis of lymphoma. The association between VTE within the first year of NHL diagnosis and candidate risk factors, including histology, was assessed with univariate analysis reported as hazard ratios (HRs) with 95% confidence intervals (CIs). The associations were then assessed using multivariate analysis with a competing risks model using the methods of Fine and Gray, accounting for death as a competing risk [20]. Candidate risk factors included: histology (DLBCL versus FL), history of prior VTE, BMI, age, race, Charlson co-morbidity score, HGB < 10 g/dL, elevated LDH, stage (stage III/IV versus I/II), presence of B-symptoms, treatment with doxorubicin, and time period during chemotherapy administration. To preserve sample size and to minimize bias, we included records with sparse missing data by creating "unknown" categories.

We calculated cumulative incidence rates of VTE in NHL per 1000 person-years over pre-specified time intervals following NHL diagnosis (0–30 days, 31–180 days, 181–365 days). Time intervals were selected based on expected clinical management course. The interval of 0–30 days was selected to represent the time period when ancillary studies were likely being done prior to therapy initiation. Given the knowledge of treatment regimens included, most patients would be off chemotherapy by 181–365 days post diagnosis. We compared rates of VTE between DLBCL and FL with confidence intervals constructed using Poisson

distribution and test-based methods using annualized incidence[21]. A two-tailed alpha significance level of less than 0.05 was used for all analyses. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

A total of 4,570 patients with NHL were identified (2,839 DLBCL; 1,731 FL), of whom 1,803 were excluded for not receiving treatment, receiving treatment outside of the VHA health system, or for receiving non-CHOP or CHOP-like therapy. Of the remaining 2,767 patients, 37 were excluded for unknown lymphoma stage. The final analytic cohort consisted of 2,730 patients (2,037 DLBCL; 693 FL) (Figure 1). The mean age at NHL diagnosis was 64 years, with the majority of the patients being male (97%), Caucasian (88%), and with a diagnosis of DLBCL (75%) (Table 1). The mean time from diagnosis to treatment initiation was 2.0 months for the entire cohort, but differed by histology: 1.3 months for DLBCL and 3.9 months for FL. During the entire follow-up period, there were 246 VTEs (192 DLBCL; 54 FL). Within the first year of NHL diagnosis, 181 patients experienced VTE (151 DLBCL; 30 FL); of which there were 34 PE, 121 DVT, and 26 with PE+DVT. Of the 151 DLBCL patients who experienced a VTE after NHL diagnosis, 9 had a history of prior VTE; while of the 30 FL patients who experienced a VTE, 1 had a history of prior VTE. The median follow-up time for the cohort was 28.4 months.

In the first 12-months following NHL diagnosis, there was an increased risk of VTE in patients with DLBCL versus those with FL with an unadjusted HR (95% CI) of 1.74 (1.18–2.58) (Table 2); however after adjusting for additional risk factors, this finding was no longer significant (adjusted HR (aHR) 1.52; 95% CI 0.97 – 2.40) (Table 3). Risk factors in multivariate analysis for development of VTE in patients with DLBCL or FL were: history of VTE before lymphoma diagnosis (aHR 4.73, 95% CI 2.47 – 9.04), time during chemotherapy administration (aHR 7.60; 95% CI 4.71 – 12.25), stage III/IV disease (aHR 1.49, 95% CI 1.05 – 2.10), BMI ≥ 30 (aHR 1.60, 95% CI 1.08 – 2.37), presence of B-symptoms (aHR 1.45, 95% CI 1.06 – 2.02), and use of doxorubicin (aHR 1.96, 95% CI 1.03 – 3.72) (Table 2). There was a possible trend toward an association between VTE and HGB < 10 g/dL (aHR 1.48, $p=0.08$). There was no significant association between risk of VTE and age, race, elevated LDH, higher comorbidity index, BMI < 18.5 , or $25 < \text{BMI} \leq 30$ in multivariate analysis.

The cumulative incidence of VTE was highest in the first 30 days following lymphoma diagnosis and decreased over time for both DLBCL and FL. Incidence of VTE per 1000-patient years in DLBCL was 271 (95% CI: 203–363) from 0–30 days, 108 (95% CI: 87–135) from 31–180 days, 35 (95% CI: 24–51) from 181–365 days, and 17 (95% CI: 11–26) from 366–730 days. Incidence of VTE per 1000-patients years in FL was 140 (95% CI: 70–280) from 0–30 days, 55 (95% CI: 33–91) from 21–180 days, 23 (95% CI: 11–48) from 181–365 days, and 20 (95% CI: 11–35) from 366–730 days. The cumulative incidence of VTE in DLBCL versus FL after adjustment in the competing risk model is presented in Figure 2 for the first 12-months following NHL diagnosis. The annualized VTE incidence rates were significantly higher in patients with DLBCL versus FL in the period from diagnosis to treatment initiation ($p<0.0001$): DLBCL 22% (95% CI: 10–29%); FL 5%

(95% CI: 2%–10%). In the 6-month period after treatment initiation, there was a trend ($p=0.08$) towards a higher VTE incidence in the DLBCL cohort: DLBCL 10% (95% CI: 8%–13%; FL 7% (95% CI: 4%–10%). During the period between 6 months to 2 years following treatment initiation, annualized incidence dropped to 2% in both cohorts and was not significantly different: DLBCL 2% (95% CI: 1%–3%; FL 2% (95% CI: 1%–3%).

DISCUSSION

In the first 12-months following NHL diagnosis, there was a 1.74-increased hazard of VTE in patients with DLBCL versus those with FL; however after adjusting for additional risk factors, this finding was no longer significant (aHR 1.52; 95% CI 0.97 – 2.40). The strongest risk factors for developing VTE included time during chemotherapy administration (aHR 7.60) and prior history of VTE (aHR 4.73). Additional risk factors for developing VTE in NHL were: advanced stage (stage III/IV), BMI ≥ 30 , presence of B-symptoms, and treatment with doxorubicin. There was no significant association between elevated LDH, decreased HGB, advancing age, black race, or higher comorbidity score and VTE. The cumulative incidence of VTE for both DLBCL and FL was highest in the 30-day period immediately following diagnosis (271 and 140 per 1000 patient-years respectively), and decreased overtime following NHL diagnosis.

Two recent studies have found an association between DLBCL histology and risk of VTE. A study of the California Cancer Registry found increased incidence of VTE in patients with intermediate/aggressive NHL (i.e. DLBCL) versus low grade NHL (i.e. FL) during the first 12-months following NHL diagnosis (4.2% and 1.8% respectively). This risk was found to be significant after adjusting for age, race, sex, stage, and co-morbidities[15]. Similarly, a Danish study found increased risk of VTE in DLBCL versus indolent lymphomas over a 12-month period (aHR 1.79; 95% CI: 1.31–2.43) [14]. Our study presents results that support these findings; however, the association between DLBCL and VTE was markedly attenuated after accounting for additional covariates. We were able to adjust for several important covariates (including prior history of VTE, type of chemotherapy, and obesity) that were not available in the earlier studies. In addition, it is possible that additional risk factors, such as presence of B-symptoms (aHR 1.45, $p=0.02$) are representative of the aggressiveness of the underlying disease and outweigh histology. Lastly, we were unable to assess FL grade. It is possible that our population contained a significant population of FL patients with grade 3b disease, which prior studies suggest should be managed similarly to DLBCL[22].

The time period following NHL diagnosis affected VTE risk: in our cohort the risk of VTE was highest in the first 30 days following NHL diagnosis and decreased over time. The greater upfront risk of VTE in NHL may correspond to the administration of chemotherapy and tumor burden. Others have found that VTE risk is related to tumor burden and time from diagnosis[14–16, 23–25]. In our study, the mean time from diagnosis to chemotherapy initiation was 2 months. We found a 7.6-fold increased risk of VTE during chemotherapy administration. These results support findings from prior studies showing an association between chemotherapy and risk of VTE [5, 26]. Given that chemotherapy is transient, its administration contributed to the higher risk of VTE early in the disease course. Standard chemotherapy regimens are typically completed over a period of 4–6 months in DLBCL and

FL. Chemotherapy is a successful treatment for NHL. The cure rate of DLBCL with standard chemotherapy is high, in some populations approaching 90% [27, 28]; similarly, the response rate for treatment of FL with standard chemotherapy is greater than 90% with the majority of patients remaining in remission for > 2 years [29, 30]. These high success rates contribute to rapid reduction in tumor burden. Thus it is plausible that the rapid reduction in disease burden in both histologies, accompanied by the high cure rate in DLBCL and the prolonged remission seen with FL contribute to the reduction in VTE risk over time.

Current VTE risk prediction models in patients with newly diagnosed or recently progressed cancer do not account for history of VTE when calculating risk [4, 8]. Prior history of VTE is a known risk factor for VTE in the general population [31]. Similarly, the Ottawa prognostic score developed to predict recurrent VTE in cancer patients, included history of prior VTE as a validated risk factor [9]. Risk of VTE in our cohort was increased over 4-fold in patients with a history of VTE. Therefore, incorporating this risk factor may assist in the identification of higher risk patients.

We found several additional risk factors for VTE in patients with NHL, some of which are not currently incorporated in available VTE risk models[4, 8]. Stage III/IV disease and obesity were associated with development of VTE. Prior studies found an association between cancer stage and risk of VTE[16, 32, 33]. However, two recent studies showed conflicting results regarding the association between stage and VTE in NHL[14, 15]. Our study supports an association between advanced stage and VTE in patients with NHL, with a 49% increase in risk associated with stage III/IV disease compared to those with stage I/II disease. As a consequence, currently available prediction models may overestimate VTE risk in patients with stage I/II DLBCL or FL, and underestimate the risk in patients with stage III/IV disease. Prior studies have not evaluated the association of BMI or prior VTE on VTE risk in NHL. Obesity is a well-described risk factor for VTE in both cancer and non-cancer populations[4, 34]. Our study supports obesity as a risk factor for development of VTE in patients with NHL.

Our study has some limitations. First, the retrospective identification of covariates from medical records limits the data available. Second, this study does not address how to categorize NHL patients in the context of the ASCO guidelines. Current guidelines[35] recommend use of a validated risk prediction model that classifies NHL as a single disease entity and this study suggests that stratification based on additional factors could improve VTE prediction. Third, although the VHA is a comprehensive care facility, some patients in the cohort may have received care outside the VHA system. Thus, it is possible VTE events were missed if diagnosed at another facility. Fourth, the VHA patient population is largely male and Caucasian, thus our findings may not be generalizable to women and/or other races. Lastly, while we used statistical methods to adjust for possible confounding, there may be residual confounding.

This study characterizes VTE risk in treated patients with the two most common histologic subtypes of NHL--DLBCL and FL. While DLBCL is a risk for VTE compared to FL, risk is attenuated by additional risk factors. Primary thromboprophylaxis is currently not the

standard of care in NHL patients; these findings provide rationale for which population of NHL patients to consider for thromboprophylaxis (those with a prior history of VTE) and the period during which thromboprophylaxis should be considered (early in diagnosis and throughout chemotherapy administration). Future studies should account for history of VTE and administration of chemotherapy when assessing VTE risk in NHL.

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REFERENCES

1. Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med*. 2000; 343:1846–1850. [PubMed: 11117976]
2. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *Journal of thrombosis and haemostasis : JTH*. 2007; 5:632–634. [PubMed: 17319909]
3. Lyman GH, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013; 31:2189–2204. [PubMed: 23669224]
4. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008; 111:4902–4907. [PubMed: 18216292]
5. Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. *PLoS medicine*. 2012; 9:e1001275. [PubMed: 22859911]
6. Mohren M, Markmann I, Jentsch-Ullrich K, Koenigsmann M, Lutze G, Franke A. Increased risk of venous thromboembolism in patients with acute leukaemia. *British journal of cancer*. 2006; 94:200–202. [PubMed: 16421591]
7. Srkalovic G, Cameron MG, Rybicki L, Deitcher SR, Kattke-Marchant K, Hussein MA. Monoclonal gammopathy of undetermined significance and multiple myeloma are associated with an increased incidence of venothromboembolic disease. *Cancer*. 2004; 101:558–566. [PubMed: 15274069]
8. Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R, et al. Prediction of venous thromboembolism in cancer patients. *Blood*. 2010; 116:5377–5382. [PubMed: 20829374]
9. Louzada ML, Carrier M, Lazo-Langner A, Dao V, Kovacs MJ, Ramsay TO, et al. Development of a clinical prediction rule for risk stratification of recurrent venous thromboembolism in patients with cancer-associated venous thromboembolism. *Circulation*. 2012; 126:448–454. [PubMed: 22679142]
10. Mohren M, Markmann I, Jentsch-Ullrich K, Koenigsmann M, Lutze G, Franke A. Increased risk of thromboembolism in patients with malignant lymphoma: a single-centre analysis. *British journal of cancer*. 2005; 92:1349–1351. [PubMed: 15798767]
11. Goldschmidt N, Linetsky E, Shalom E, Varon D, Siegal T. High incidence of thromboembolism in patients with central nervous system lymphoma. *Cancer*. 2003; 98:1239–1242. [PubMed: 12973848]
12. 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. *Thrombosis research*. 2012; 130:e6–e12. [PubMed: 22507288]
13. Komrokji RS, Uppal NP, Khorana AA, Lyman GH, Kaplan KL, Fisher RI, et al. Venous thromboembolism in patients with diffuse large B-cell lymphoma. *Leukemia & lymphoma*. 2006; 47:1029–1033. [PubMed: 16840193]

14. Lund JL, Ostgard LS, Prandoni P, Sorensen HT, de Nully Brown P. Incidence, determinants and the transient impact of cancer treatments on venous thromboembolism risk among lymphoma patients in Denmark. *Thrombosis research*. 2015; 136:917–923. [PubMed: 26371409]
15. Mahajan A, Wun T, Chew H, White RH. Lymphoma and venous thromboembolism: influence on mortality. *Thrombosis research*. 2014; 133(Suppl 2):S23–S28. [PubMed: 24862141]
16. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *Jama*. 2005; 293:715–722. [PubMed: 15701913]
17. Blom JW, Vanderschoot JP, Oostindier MJ, Osanto S, van der Meer FJ, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. *Journal of thrombosis and haemostasis : JTH*. 2006; 4:529–535. [PubMed: 16460435]
18. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. *Journal of clinical epidemiology*. 1993; 46:1075–1079. discussion 81–90. [PubMed: 8410092]
19. Sanfilippo KM, Wang TF, Gage BF, Liu W, Carson KR. Improving accuracy of International Classification of Diseases codes for venous thromboembolism in administrative data. *Thrombosis research*. 2015
20. Fine GG, R. A proportional hazards model for the subdistribution of a competing risk. *J Am Statistical Association*. 1999; 94:496–509.
21. Sahai HK, A. *Statistics in Epidemiology: Methods, Techniques and Applications*. CRC Press LLC; 1995.
22. Bartlett NL, Rizeq M, Dorfman RF, Halpern J, Horning SJ. Follicular large-cell lymphoma: intermediate or low grade? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1994; 12:1349–1357. [PubMed: 8021725]
23. Alcalay A, Wun T, Khatri V, Chew HK, Harvey D, Zhou H, et al. Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006; 24:1112–1118. [PubMed: 16505431]
24. Cronin-Fenton DP, Sondergaard F, Pedersen LA, Fryzek JP, Cetin K, Acquavella J, et al. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997–2006. *British journal of cancer*. 2010; 103:947–953. [PubMed: 20842120]
25. Walker AJ, Card TR, West J, Crooks C, Grainge MJ. Incidence of venous thromboembolism in patients with cancer - a cohort study using linked United Kingdom databases. *European journal of cancer*. 2013; 49:1404–1413. [PubMed: 23146958]
26. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Archives of internal medicine*. 2000; 160:809–815. [PubMed: 10737280]
27. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *The New England journal of medicine*. 2002; 346:235–242. [PubMed: 11807147]
28. Flinn IW, van der Jagt R, Kahl BS, Wood P, Hawkins TE, Macdonald D, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood*. 2014; 123:2944–2952. [PubMed: 24591201]
29. Federico M, Luminari S, Dondi A, Tucci A, Vitolo U, Rigacci L, et al. R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013; 31:1506–1513. [PubMed: 23530110]
30. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grunhagen U, Losem C, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013; 381:1203–1210. [PubMed: 23433739]

31. Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. *Archives of internal medicine*. 2000; 160:3415–3420. [PubMed: 11112234]
32. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Archives of internal medicine*. 2006; 166:458–464. [PubMed: 16505267]
33. White RH, Chew HK, Zhou H, Parikh-Patel A, Harris D, Harvey D, et al. Incidence of venous thromboembolism in the year before the diagnosis of cancer in 528,693 adults. *Archives of internal medicine*. 2005; 165:1782–1787. [PubMed: 16087828]
34. Pomp ER, le Cessie S, Rosendaal FR, Doggen CJ. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. *Br J Haematol*. 2007; 139:289–296. [PubMed: 17897305]
35. Lyman GHK AA, Falanga A, Clarke-Pearson D, Flowers C, Jahanzeb M, Kakkar A, Kuderer NM, Levine MN, Liebman H, Mendelson D, Raskob G, Somerfield MR, Thodiyil P, Trent D, Francis CW. American Society of Clinical Oncology Guideline: Recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *Journal of Clinical Oncology*. 2007; 25:5490–5505. [PubMed: 17968019]

Highlights

- Competing risk analysis is used to identify risks for venous thromboembolism in lymphoma.
- Diffuse large B-cell lymphoma is associated with increased risk of thrombosis.
- Time during chemotherapy and history of thrombosis are the strongest risks for thrombosis.
- Risk of venous thromboembolism is highest immediately following lymphoma diagnosis.

Figure 1.

Consort Diagram, DLBCL/FL between 1998 and 2008 treated with R-CHOP/CHOP-like Regimens

DLBCL = diffuse large B cell lymphoma; FL = follicular lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; R = rituximab; Veterans Health Administration

No. at Risk

DLBCL	2037	1800	1626	1495	1385
FL	693	661	635	615	602

FIGURE 2.
Cumulative Incidence of VTE in DLBCL versus FL in the first 12-months after NHL
Diagnosis

Table 1

Demographic and Clinical Characteristics stratified by NHL type

Characteristics	NHL type			P-value
	Overall (N=2730)	DLBCL (n=2037)	FL (n=693)	
Mean Age (years)	64.4	64.8	63.1	0.0002
Age over 60 (%)	61.4	62.7	57.4	0.01
Sex (Male %)	96.9	97.2	96.1	0.15
Race (%)				0.02
White	87.8	87.3	89.0	
Black	10.6	11.3	8.5	
Other	1.6	1.3	2.5	
Stage (%)				<0.0001
I/II	37.7	41.9	25.1	
III/IV	62.3	58.1	74.9	
LDH (%)				<0.0001
Elevated	50.2	56.5	31.6	
Normal	42.9	37.4	59.2	
Unknown	7.0	6.2	9.2	
B-symptoms (%)				<0.0001
Yes	47.0	50.2	37.5	
No	48.5	45.3	57.7	
Unknown	4.5	4.5	4.8	
HGB (%)				
>=10	73.4	76.5	72.4	<0.0001
<10	9.2	5.5	10.5	
Unknown	17.4	18.0	17.2	
WBC				p=0.18
>=11,000	11.0	11.8	8.4	
<11,000	66.8	69.0	60.3	
Unknown	22.2	19.2	31.3	
VTE before NHL (%)	1.6	1.6	1.4	0.75
CHOP Treatment (%)	85.4	94.0	60.2	<0.0001
Co-morbidity score (mean)	2.3	2.4	1.8	<0.0001
BMI at Tx groups (%)				<0.0001
BMI < 18.5	2.3	2.6	1.6	
18.5 <= BMI < 25	32.2	34.4	25.8	
25 <= BMI < 30	36.4	36.6	35.8	
BMI>=30	25.0	23.8	28.4	
Unknown	4.1	2.7	8.4	

NHL = Non-Hodgkin lymphoma; DLBCL = diffuse large B cell lymphoma; FL = follicular lymphoma; LDH = lactate dehydrogenase; B-symptoms = fever (> 38°C), drenching night sweats, or 10% loss in body weight in the 6 months preceding diagnosis; HGB = hemoglobin; WBC

= white blood cell count; VTE = venous thromboembolism; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; BMI = body mass index

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Table 2

Univariate Analysis of Risk Factors for VTE in NHL in the First Year of NHL Diagnosis

Variable	Unadjusted Hazard Ratio	95% Confidence Interval	p value
Histology			
FL	Referent		
DLBCL	1.74	1.18, 2.58	0.01
History of VTE	4.00	2.12, 7.51	<0.0001
Body Mass Index			
BMI < 18.5	1.46	0.58, 3.69	0.42
18.5 BMI < 25	Referent		
25 BMI < 30	1.26	0.87, 1.81	0.22
BMI 30	1.44	0.98, 2.11	0.07
Age	1.00	0.99, 1.01	0.96
Race			
Caucasian	Referent		
African American	0.93	0.59, 1.51	0.76
Other	0.68	0.17, 2.79	0.59
Comorbidity Index	1.00	0.94, 1.06	0.92
Laboratory Data			
HGB < 10g/dL	1.70	1.12, 2.58	0.01
Elevated LDH (> ULN)	1.35	0.99, 1.83	0.06
Disease Characteristics			
Stage III/IV versus I/II	1.53	1.11, 2.11	0.01
B-Symptoms	1.56	1.15, 2.11	0.004
Treatment Characteristics			
CHOP versus CVP	2.25	1.28, 3.96	0.01
During Chemotherapy	7.44	4.84, 11.44	<0.0001

VTE = venous thromboembolism; NHL = Non-Hodgkin lymphoma; BMI = body mass index; HGB = hemoglobin; LDH = lactate dehydrogenase; ULN = upper limit of normal; B-symptoms = fever (> 38°C), drenching night sweats, or 10% loss in body weight in the 6 months preceding diagnosis; DLBCL = diffuse large B cell lymphoma; FL = follicular lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP = cyclophosphamide, vincristine, and prednisone.

Table 3

Competing Risk Model for Risk Factors for VTE in NHL in the First Year of NHL Diagnosis

Variable	Adjusted Hazard Ratio	95% Confidence Interval	p value
Histology			
FL	Referent		
DLBCL	1.52	0.97, 2.40	0.07
History of VTE	4.73	2.47, 9.04	<0.0001
Body Mass Index			
BMI < 18.5	1.05	0.39, 2.78	0.93
18.5 BMI < 25	Referent		
25 BMI < 30	1.34	0.93, 1.94	0.12
BMI 30	1.60	1.08, 2.37	0.02
Age	1.00	0.98, 1.01	0.70
Race			
Caucasian	Referent		
African American	0.83	0.50, 1.37	0.46
Other	0.81	0.19, 3.40	0.77
Comorbidity Index	0.96	0.89, 1.03	0.21
Laboratory Data			
HGB < 10g/dL	1.48	0.95, 2.32	0.08
Elevated LDH (> ULN)	0.87	0.61, 1.23	0.43
Disease Characteristics			
Stage III/IV versus I/II	1.49	1.05, 2.10	0.02
B-Symptoms	1.45	1.06, 2.00	0.02
Treatment Characteristics			
CHOP versus CVP	1.96	1.03, 3.72	0.04
During Chemotherapy	7.60	4.71, 12.25	<0.0001

VTE = venous thromboembolism; NHL = Non-Hodgkin lymphoma; BMI = body mass index; HGB = hemoglobin; LDH = lactate dehydrogenase; ULN = upper limit of normal; B-symptoms = fever (> 38°C), drenching night sweats, or 10% loss in body weight in the 6 months preceding diagnosis; DLBCL = diffuse large B cell lymphoma; FL = follicular lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP = cyclophosphamide, vincristine, and prednisone.