Thrombotic risk assessment in adult patients with lymphoid malignancies in Benin City: A cross sectional study.

Juliet I Uduebor, Benedict Nwogoh

Abstract

Background: Venous thromboembolism (VTE) is a major cause of morbidity and mortality in cancer patients. Thromboprophylaxis can be used to prevent VTE in patients with malignany. Risk assessment models (RAM) can be used to identify those who may benefit from thromboprophylaxis. The study aims to determine the cancer associated thrombotic risk of patients with lymphoid malignancies.

Methods: This was a case control study conducted at the Department of Haematology and Blood Transfusion, University of Benin Teaching Hospital, (UBTH) Benin City. Eighty two patients, 18 years and above with lymphoid malignancies and 82 controls were evaluated using the Khorana risk assessment model. Data was analyzed using SPSS version 21.

Results: The ages of patients and controls were 54.0 ±14.0 vs. 50.0±11.0 years, p = 0.06 respectively. They included 41 (50.0%) males in the patient group and 43(52.4%) males in the controls (p =0.76). The commonest types of lymphoid malignancies amongst them were Non-Hodgkin's lymphoma (NHL) 32 ((39.0%), multiple myeloma (MM) 24 (29.3%) and chronic lymphocytic leukaemia/small lymphocytic lymphoma CLL/SLL 18 (21.9%). Patients with lymphoid malignancies had significantly higher risk scores compared to the controls. Majority of the patients have intermediate risk and 3.7% were at high risk of cancer associated thrombosis. Thirteen (15.9%) of the controls had intermediate risk while 69 (84.1%) had low risk. Patients with chronic lymphoid leukaemia/small lymphocytic lymphoma and non-Hodgkin's lymphoma had the high risk status.

Conclusion: Thrombotic risk is largely intermediate in patients with lymphoid malignancies and thus may not require routine thromboprophylaxis. However individualized risk assessment based on the presence of additional prothrombotic factors should be considered to determine patients with lymphoid malignancies that may benefit from thromboprophylaxis.

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Introduction

Malignancies including lymphoid neoplasms are associated with increased risk of venous thrombo-embolism (VTE). The relative risk of VTE in cancer patients is estimated at 4 – 7 fold higher compared to the general public or patients without cancer.[1, 2]VTE comprising pulmonary embolism (PE) and deep vein thrombosis (DVT)is a major cause of morbidity and the second leading cause of mortality among cancer patients.[3,4]

Cancer is a hypercoagulable and prothrombotic disease associated with significant alteration of the haemostatic system. The pathogenesis of thrombosis in cancer is associated with the release of tissue factor (TF), expression of activated factor X and procoagulant microparticles by the cancer cells.[4] There is also increased expression of plasminogen activator inhibitor-1 (PAI-1), urokinase plasminogen and tissue-type plasminogen activators creating an imbalance between activators and inhibitors of fibrinolysis.[4] Cancer cells also secrete cytokines such as TNF-α and IL-1β, which stimulate the expression of TF and down-regulate thrombomodulin This impairs the activation of protein C.[4]

The risk of cancer associated thrombosis is variable but can be classified as patient related and cancer related. Cancer related factors include cancer type, stage of the disease, treatment associated risk such as use of immunomodulators, chemotherapy or hormonal therapy and use of central venous line.[4] Haematological malignancy which comprises lymphoid and myeloid malignancies is ranked the fourth leading type of cancer associated with increased thrombotic risk.[3] Lymphoid malignancies especially myeloma and aggressive lymphomas have relatively higher risk of cancer associated thrombosis compared to other haematologic malignancies.[5]

Based on the risk status attributed to these malignancies, it is common practice among clinicians to recommend thromboprophylaxis for patients without standard risk assessment. Nwogoh et al[6] reported a high rate of practice of thromboprophylaxis for patients with haematological malignancies in Nigeria without a standard risk assessment. Ewere et al[7] reported that over 70% of clinicians do not conduct thrombotic risk assessment before commencing chemotherapy and furthermore less than 20% follow standard guidelines for thromboprophylaxis. A standard risk assessment model for cancer associated thrombosis such as the Khorana

Department of Haematology and Blood Transfusion University of Benin Teaching Hospital, Benin City.

All correspondences to:
Dr. Benedict Nwogoh
Email: benedict.nwogoh@uniben.edu

risk assessment model has been developed.[8] This model has been approved for use by the International Society for Thrombosis and Haemostasis (ISTH), American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) to provide guide for the use of thromboprophylaxis against cancer associated thrombosis in ambulatory cancer patients.[9-11]The Nigerian Society of Haematology and Blood Transfusion have recommended the use of the same guideline in the management of VTE.[12]The VTE risk score categories using the Khorana model have been found to correlate with the development of VTE and with overall survival in patients with cancer who are undergoing chemotherapy.[5]

Bleeding is a significant risk factor associated with the use of antithrombotic agents in thromboprophylaxis especially in patients with cancer.[4]Therefore proper risk stratification is necessary in selecting patients that will benefit from thromboprophylaxis. The objective of this study was to determine the cancer associated thrombosis risk status of patients with lymphoid malignancies seen at the University of Benin Teaching Hospital, Benin City using the Khorana risk assessment model and to provide a justification for the use of thromboprophylaxis.

Patients and Methods

Study design

This study was a cross sectional study.

Study setting

The study was conducted at the Haematology Department, University of Benin Teaching Hospital (UBTH), Benin City. UBTH is a Federal Government owned tertiary institution with over 800 bed capacity, situated in Egor LGA, Benin City, Edo State. It receives referrals from neighbouring states such as Delta, Ondo, kogi and Bayelsa.

Study population

The study participants comprised patients diagnosed with lymphoid malignancies based on peripheral blood film report, bone marrow aspiration cytology, lymph node tissue histology, and immunohistochemistry.

Sample size determination

Sample size was estimated using the formula for cross sectional study[13]

$$N = \frac{Z^2 Pq}{d^2}$$

Where: N=Minimum sample size

z=Standard normal deviation (1.96)

P=Prevalence of lymphoid haematological malignancies

q= 1-P

d= degree of precision used (0.05)

Based on the prevalence of lymphoid malignancies of 5.7% reported by Nwanadi et al[14] in a study in Benin City, a sample size of 82 was reached. Eighty two subjects with lymphoid malignancies were recruited consecutively from the haematology clinic while 82 apparently healthy individuals were recruited from the general public to serve as controls.

Inclusion and exclusion criteria

Study inclusion criteria for the patient group included age 18 years and above and presence of a lymphoid malignancy. The controls included adults of similar age group in apparent good health. Excluded were patients with myeloid malignancies and patients on anticoagulant therapy.

Study duration

The study was conducted between May 2018 and June 2019.

Study instrument

The study instrument was based on the 5 clinical and laboratory parameters defined by the Khorana risk assessment model.[8] The parameters include primary tumor site, body mass index, haemoglobin, white blood cell count and platelet count. Score is assigned as follows: Primary tumor site (+1 or 2 points), platelet count of $350x10^9$/L or more (+1 point), hemoglobin concentration of 100 g/L or lower or use of erythropoiesis-stimulating agents (+1 point), leukocyte count of $11x10^9$/L or higher (+1 point), and a body mass index of $35kg/m^2$ or higher (+1 point). A sum score of 0 points classifies patients as being at low risk of VTE, 1 or 2 points at intermediate risk, and those with 3 or more points at high risk.

The heights and weights of consenting participants were measured with a stadiometer and thereafter three millilitres of venous blood was collected aseptically from the antecubital veins. The blood was dispensed into an ethylenediamine tetra-acetic acid container and use for full blood count (FBC). Full blood count was carried out using a 3 part automated haematology analyzer (Sysmex model KN21).

Ethical consideration

This study was approved by the Institutional Health Research and Ethical committee of University of Benin Teaching Hospital. Written informed consent was sought and obtained from all participants in the study.

Statistical analysis

Data was analyzed with the Statistical Package for Social Science version 21. The anthropometric indices and full

blood counts were summarized as mean and standard deviation. The differences in mean between the patients and controls were compared using the student t test. The risk scores were summarized as median and interquartile range. Difference in median scores between patients and controls as well as between two subtypes of lymphoma groups were compared using Mann Whitney U test. Median scores across the lymphoma groups was compared using Kruskal-Wallis test. The thrombotic risk status was compared between patient and control groups using the Fisher's test. P value was set at 0.05.

Result

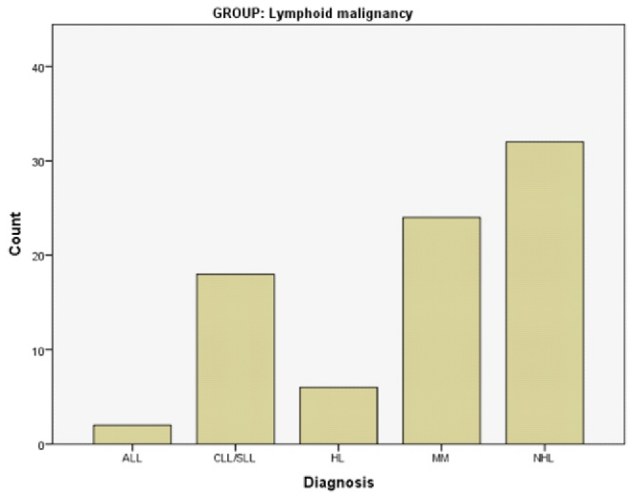
A total of 164 subjects comprising of 82 patients with lymphoid neoplasm and 82 controls participated in the study. The patients with lymphoid malignancies consist of 41 (50.0%) males and 41(50.0%) females while the controls included 43(52.4%) males and 39 (47.6%) females.

The age of patients with lymphoid neoplasm ranged from 18 – 85 years with a mean age of 54 ±14years. The controls age ranged from 20 – 68 years with a mean age of 50 ±11years. The difference in mean age was not statistically significant (p = 0.06). (Table 1)

Table 1: Demographics of the study subjects

	Lymphoid neoplasm n (%)	Controls n (%)	χ^2	P value
Age group				
<30	4 (4.9)	4 (4.9)		
30 - 39	10 (12.2)	10 (12.2)	3.256	0.52
40 - 49	9 (11.0)	16 (19.5)		
50 - 59	30 (36.6)	31 (37.8)		
≥60	29 (35.4)	21 (25.6)		
Sex				
Male	41(50.0)	43(50.0)		
Female	41(50.0)	39(47.6)	0.098	0.76
Employment status				
Dependent	23(28.0)	4(4.9)		
Employed	29(35.4)	60(73.2)	27.168	<0.01
Self Employed	30(36.6)	18(21.9)		
Educational status				
None	4(4.9)	0(0)		
Primary	12(14.6)	5(6.1)	8.530	0.03
Secondary	17(20.7)	15(18.3)		
Tertiary	49(59.8)	62(75.6)		

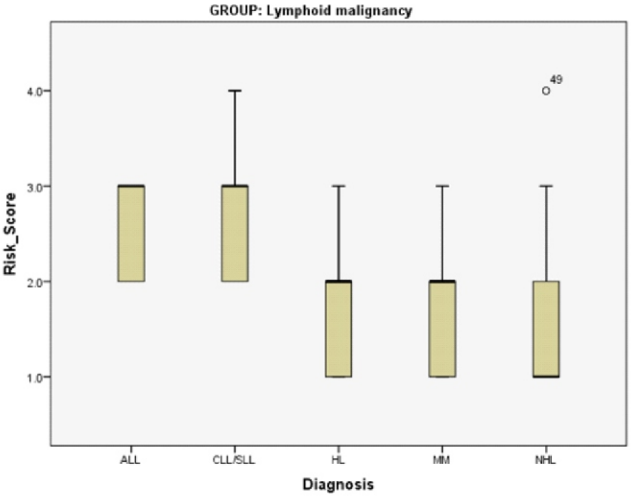
The employment and educational status of the patients with lymphoid neoplasm showed that thirty (36.6%) were self-employed and twenty three (28.0%) were dependents. Majority, 49 (59.8%) attained tertiary level of education. Forty six (56.1%) of the subjects with lymphoid neoplasm were on chemotherapy (Table 2).



HL: Hodgkin's lymphoma; MM: Multiple myeloma; NHL: Non-Hodgkin's lymphoma; CLL/SLL: Chronic lymphocytic leukaemia/small lymphocytic lymphoma; ALL: Acute lymphocytic leukaemia

Figure 1: Bar chart showing distribution of the various lymphoid malignancies

Figure 1 shows the spectrum of lymphoid malignancies among the patients. The commonest type of neoplasm among the subjects was Non-Hodgkin's lymphoma (NHL) accounting for 32 ((39.0%), followed by multiple myeloma (MM) 24 (29.3%) and chronic lymphocytic leukaemia/small lymphocytic lymphoma CLL/SLL 18 (21.9%).



HL: Hodgkin's lymphoma; MM: Multiple myeloma; NHL: Non-Hodgkin's lymphoma; CLL/SLL: Chronic lymphocytic leukaemia/small lymphocytic lymphoma; ALL: Acute lymphocytic leukaemia

Figure 2: Boxplot of the risk scores of the various lymphoid malignancies (p = 0.001)

There was no significant difference in the mean weight of patients and controls (62.4±1.2 vs. 64.5±5.8kg, p = 0.13). The patients had a significantly higher mean height (1.63±0.08 vs. 1.60±0.05m, p = 0.01). The body mass index was significantly reduced in the patient group (23.6±4.5 vs.25.2 ± 2.5kg/m², p < 0.01). Three (3.7%) of the patients with lymphoid malignancy were obese but none of the controls was obese (p = 0.25) (Table 2).

Table 2: Anthropometric, Haematological and Coagulation Parameters of Study Subjects

	Lymphoid neoplasm Mean ± SD	Control Mean ± SD	t test	P value
Age (yrs)	54.3±13.7	50.2±11.1	3.887	0.06
Weight (Kg)	62.4±11.2	64.5±5.8	-1.513	0.13
Height (m)	1.63±0.08	1.60±0.48	2.609	0.01
BMI (kg/m^2)	23.6±4.5	25.2±2.5	-2.822	0.01
Hb (g/dL)	10.2±2.1	13.3±1.7	-10.59	<0.01
HCT (%)	30.9±5.5	39.3±5.0	-10.31	<0.01
WBCx10^{9}cells/L	34.2±7.4	4.8±1.2	3.465	0.01
Plt x10^{9}cells/L	208.9±14.2	207.1±6.8	0.104	0.92

The mean haemoglobin was significantly reduced in the patient group compared to the controls (10.2±2.1 vs. 13.3±1.7g/dL, p < 0.01). Thirty eight of the patients with lymphoid neoplasm had haemoglobin values of less than 10g/dL while none of the controls had haemoglobin below 10g/dL. The mean total white blood cell count was significantly increased in the patient group than in the controls (34.2±7.4 x 10^9/L vs. 4.8±1.2x 10^9/L, p < 0.01). Twenty six (31.7%) of patients with lymphoid malignancies had WBC count >15,000 x 10^9/L while none of the controls had WBC count above 15,000 x 10^9/L; the difference in the proportion leucocytosis was statistically significant (p < 0.01). The mean platelet count was not significantly different between patients with lymphoid neoplasm and the controls (208.9±14.2 vs. 207.1±6.8 x 10^9/L; p = 0.92) (Table 2).

The median (interquartile range) risk score was significantly higher in the lymphoid malignancy patients compared to the controls (2.0 (1.0 – 2.0) vs. 0.0 (0.0 – 0.0), p < 0.01). There was a statistically significant difference in the median risk scores across the group of lymphoid neoplasm (p <0.01) (Figure 2). Comparison of median scores between subtypes of lymphoma showed that patients with CLL/SLL had significantly higher risk scores compared to those with Hodgkins Lymphoma (p <0.01), Multiple Myeloma (p<0.01) and Non-Hodgkins Lymphoma (p<0.01) (Table 3).

Table 3: Comparison of mean difference of Risk scores between different lymphoid malignancies

Ref Group	Median (IQR)	Comp Group	Median (IQR)	P value
HL	1.5 (1.0 - 2.3)	MM	2.0 (1.0 - 2.0)	0.90
		NHL	1.0 (1.0 - 2.0)	0.89
		CLL/SLL	3.0 (2.0 - 3.0)	<0.01
		ALL*	2.5	0.29
MM	2.0 (1.0 - 2.0)	HL	1.5 (1.0 - 2.3)	0.90
		NHL	1.0 (1.0 - 2.0)	0.42
		CLL/SLL	3.0 (2.0 - 3.0)	<0.01
		ALL*	2.5	0.19
NHL	1.0 (1.0 - 2.0)	HL	1.5 (1.0 - 2.3)	0.89
		MM	2.0 (1.0 - 2.0)	0.42
		CLL/SLL	3.0 (2.0 - 3.0)	<0.01
		ALL*	2.5	0.18
CLL/SLL	3.0 (2.0 - 3.0)	HL	1.5 (1.0 - 2.3)	<0.01
		MM	2.0 (1.0 - 2.0)	<0.01
		NHL	1.0 (1.0 - 2.0)	<0.01
		ALL*	2.5	0.83
ALL*	2.5	HL	1.5 (1.0 - 2.3)	0.29
		MM	2.0 (1.0 - 2.0)	0.19
		NHL	1.0 (1.0 - 2.0)	0.18
		CLL/SLL	3.0 (2.0 - 3.0)	0.83

HL: Hodgkin's lymphoma; MM: Multiple myeloma; NHL: Non-Hodgkin's lymphoma; CLL/SLL: Chronic lymphocytic leukaemia/small lymphocytic lymphoma; ALL: Acute lymphocytic leukaemia

*ALL has 2 samples hence no IQR.

Table 4: Comparison of Risk Score between Therapy Naïve and Patients on Therapy for each subtype of lymphoid neoplasm

Variable	Disease subtype	N	Therapy naïve Median (IQR)	N	On therapy Median (IQR)	P value
Risk score	HL	1	2.00	5	1.0 (1.0 - 2.5)	0.67
	MM	7	1.0 (1.0 - 2.0)	17	2.0 (1.0 - 2.0)	0.95
	NHL	18	1.0 (1.0 - 2.0)	14	1.5 (1.0 - 2.0)	0.75
	CLL/SLL	8	3.0 (2.3 - 3.8)	10	2.0 (2.0 - 3.0)	0.12
	ALL	1	3.00	1	2.00	1.00

HL: Hodgkin's lymphoma; MM: Multiple myeloma; NHL: Non-Hodgkin's lymphoma; CLL/SLL: Chronic lymphocytic leukaemia/small lymphocytic lymphoma; ALL: Acute lymphocytic leukaemia

Table 4 compares median risk scores between patient that are therapy naïve and patient on therapy for each subtype of lymphoid malignancy. There was no significant difference in their mean scores (p >0.05).

The thrombotic risk stratification based on Khorana risk scores showed that 79 (96.3%) patients with lymphoid neoplasm had intermediate risk and 3 (3.7%) high risk.[8]Two of the three patients with high risk had

CLL/SLL and one had NHL. In the control group 12 (14.6%) had intermediate risk, while 70 (85.4%) had low risk. The risk status was significantly higher in the patients with lymphoid neoplasm ($p < 0.01$).

Discussion

The risk of thrombosis and the benefits of thromboprophylaxis are clearly established in patients with cancer. However the use of thromboprophylaxis is associated with increased risk of bleeding.[15, 16] Therefore, proper selection of patients using appropriate risk model is important. The index study using the Khorana risk assessment model has established that patients with lymphoid malignancy have a relatively higher risk status for thrombosis compared to the control population. This is consistent with several reports in literature that found patients with cancer to have several folds increased risk of thrombosis.[1,2]

Majority of patients with lymphoid malignancies have intermediate risk of cancer associated thrombosis and thus may not require thromboprophylaxis. Only 3.7% of the study population have high risk of cancer associated thrombosis and thus may require thromboprophylaxis. Among the various subtypes of chronic lymphoid neoplasm, CLL/SLL patients had the highest risk scores followed by multiple myeloma and non-Hodgkins's lymphoma. Multiple myeloma patients were found to have intermediate risk. However a number of studies have reported increased incidence of VTE in multiple myeloma patients.[17 - 19] The variation is attributed to the fact that the model focused on cancer associated risk alone. Increased thrombosis in myeloma patients is attributed to the effect of treatment with agents such as immunomodulators and steroids, and other myeloma disease related morbidity such as immobilization due to skeletal complications.[17 - 19] The patients with lymphoma including NHL and Hodgkin's were found to have intermediate risk. Lymphoma is a heterogeneous disease and thrombotic risk has been reported to be higher in patients with aggressive subtypes and those with bulky disease.[20] The scope of investigations available locally may not allow for precise classification of lymphoma type based on tumor behavior. Thus it is most likely that the intermediate risk found in most of the lymphoma patients may be because they had an indolent disease subtype.

Although over fifty percent of the patients had commenced treatment however the risk score did not differ significantly between those already on treatment and those yet to commence treatment. In some instances as mentioned above, treatment with some chemotherapy and immunotherapeutic agents may accentuate patient thrombotic risk.[18, 19] Patients with acute leukaemia on therapy with L-asparaginase have a higher risk of thrombosis compared to those treated without it.[21] In addition to the cancer associated risk of thrombosis, the effect of therapeutic agents and other non-cancer related risk of thrombosis should be considered in contemplating the need for thromboprophylaxis.

The strength of the study is that it is one of the few studies that evaluated cancer associated thrombotic risk in Nigeria using a risk assessment model. The parameters used in this model are basic clinical and laboratory parameters that are easily measurable and widely available. It is cheap and does not require sophisticated instrument. Thus, the model can be easily adopted by clinicians practicing in remote settings for the management of cancer patients.

The limitation of the study and the model is that it focused on only cancer associated risk of thrombosis. It is important to state that a number of risk factors for thrombosis other than cancer exist and was not considered in the model. Factors including genetic risk factors such as factor V Leiden, protein C and S deficiency, antithrombin deficiency and other patient related conditions such as diabetes, hypertension, dyslipidaemia, smoking, use of hormonal contraceptives, antiphospholipid syndrome, immobility among others may further increase the risk of thrombosis and thus should be considered where present in taking a decision on thromboprophylaxis.[12,22] Secondly, there is limited capacity to precisely characterize and classify lymphoma in Nigeria. It is possible that patients with CLL/SLL with high risk may have variants of aggressive lymphoma.

In conclusion, this study has demonstrated that only 3.7% of patients with lymphoid neoplasm have high risk of cancer associated thrombosis that will require thromboprophylaxis. However, the decision to administer thromboprohylaxis should be individualized based on the presence of additional risk factors.

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