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Thrombotic Risk in Patients with Breast Cancer Using Soluble P-Selectin and Modified Khorana Risk Assessment Model in Nnamdi Azikiwe University Teaching Hospital, NNEWI, Anambra State

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Abstract

Background: Venous Thromboembolism (VTE) is a cause of increased morbidity and mortality in cancer patients. VTE is the second leading cause of death in cancer patients. Risk assessment models have been developed to identify patients at risk of VTE for thromboprophylaxis. Risk scores of patients in our environment have not been adequately investigated.

Objective: The study evaluates the association of thrombotic risk assessment scores (using the modified Khorana risk assessment tool) and soluble P-selectin levels with thrombotic events in patients with breast cancer and to compare rates of thrombotic events between the breast cancer population and controls.

Methods: This is a comparative cross-sectional study conducted at Nnamdi Azikiwe University Teaching Hospital (NAUTH, Nnewi, Anambra State). Study population consists of 2 groups (breast cancer and controls) with 45 and 20 subjects respectively. The modified Khorana risk assessment score was used to assess cancer associated thrombotic risk. sP-selectin levels were also analyzed and compared between the study groups. The study was approved by the institutional ethical review committee. Data was analyzed with SPSS version 23, P value ≤ 0.05.

Result: The age of individuals with breast cancer ranged from 30 to 74 years with a mean and standard deviation of 46.8 ± 11.4 years while the controls had an age range of 31 to 69 years with a mean and standard deviation of 47.7 ± 11.1 years. The differences in mean was not statistically significant (p=0.774).

Forty-four (97.8%) individuals with BRCA had intermediate risk score and 1 (2.2%) had high risk score while 9 (45.0%) of the controls were intermediate risk and 11 (55.0%) low risk. The difference in proportion of risk category was statistically significant (p=0.000).

The median (IQR) levels of soluble P-selectin in individuals with BRCA and controls were 12.0 (10.1-23.9) ng/mL and 7.7 (5.5-9.6) ng/mL respectively. There was a statistically significant difference in the median (p=0.001).

A total of 2 (2.2%) subjects with VTE related symptoms had deep Vein Thrombosis (VTE) confirmed by Doppler scan.

Conclusion: The study has demonstrated that patients with breast cancer have moderate to high-risk scores for cancer associated thrombosis using the modified Khorana risk model. The rate of DVT in breast cancer patients in the study was increased as compared with the controls.

Keywords: Venous thromboembolism; Soluble P-selectin; Khorana risk assessment tool; DVT; Breast cancer

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Introduction

The relationship between cancer and thrombosis has long been established since the days of Armand Trousseau 1865, who first described the clinical association between idiopathic Venous Thromboembolism (VTE) and occult malignancy [1]. Cancers are associated with hypercoagulability; however, bleeding is also a common occurrence in cancer patients. Venous Thromboembolism

(VTE), including Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), is a common complication of malignancy [2]. Thrombosis in cancer patients is associated with increased morbidity and mortality.

Cancer patients have a 2-7-fold increased risk of developing VTE compared to patients without cancer [3]. This was seen in a retrospective study on VTE in cancer patients by Khorana et al. which reported a prevalence rate of 4.1% [3]. In another study design, (cohort study) of 17,284 cancer patients in the US between 2004 and 2009, Khorana et al. reported a higher VTE rate of 12.6% [4]. This suggests that burden of VTE in cancer patients may vary with study design and the higher incidence in prospective studies (such as the cohort) tend to reflect the high burden of CAT (Cancer Associated Thrombosis). Sotumbi et al. in University College Hospital, Ibadan reported a rate of 2.9% in a retrospective postmortem study of cancer patients [5]. This can be compared with its prevalence which varied between 2.4% and 9.6% in postoperative patients, and between 380 and 448 per 100,000 births per year in pregnant and postpartum women which are non-cancer patients [6].

The mechanisms underlying hypercoagulability in cancer patients include tumor cell-specific clot-promoting properties, which may also contribute to the process of tumor growth and dissemination; therapy related risk and host risk factors [7]. Tumor specific risks include: expression of Tissue Factor (TF) by tumor cells, production of Microparticles (MP), inflammatory cytokines by tumor and/or host cells, and direct adhesion of tumor cells to platelets, leukocytes, and endothelial cells.

Prediction models for chemotherapy-associated VTE suggest that risk factors including those related to the tumor (tumor type, clinical stage, chemotherapy, use of anti-angiogenic drugs or erythropoietic growth factors, and insertion of central venous catheters), and those related to individual patient characteristics (sex, race, age, previous VTE history, immobilization, and obesity) as well as biological markers, such as leukocyte and platelet counts and circulating levels of Tissue Factor (TF), P-selectin, and D-dimer can be used to predict the risk of VTE and high risk patients can receive appropriate intervention. Inclusion of biomarker such as P-selectin in risk assessment models may increase the ability of such model to establish causal relationship between VTE and cancer since it is highly available. It is anticipated that targeted thromboprophylaxis based on outcome of predictive models may improve risk-benefit ratio in patients [8].

Many lines of evidence suggest that P-selectin, which is a member of the selectin family of cell adhesion molecules, might play an important role in the interrelation between cancer and thrombosis. P-selectin, which is found in α granules of platelets and the Weibel-Palade bodies of endothelial cells is expressed on the cell surface on activation, mediates the adhesion of cancer cells in thrombosis, cancer growth and metastasis [9]. The interaction of P-selectin with CD24 on all neoplastic cancer cells allows their interaction with platelets and their adherence to endothelium in the process of metastatic spread [10]. Recent studies have demonstrated that high plasma levels of soluble P-selectin (sP-selectin) are strongly associated with VTE [11,12].

The VTE risk is variable with cancer type. Studies have reported higher rates in solid cancers compared to hematological malignancies with physicians more concerned for bleeding rather than thrombotic complications in patients with hematological malignancies; however, this report [13] highlighted significant VTE event rates seen in patients with lymphomas and multiple myeloma [13]. Khorana reported higher rates in solid organ cancers including pancreas, kidneys and ovary relative to myeloma and lymphoma; however, the burden of multiple myeloma and lymphoma in most population seem to exceed the mentioned solid organ tumors [3]. There is paucity of literature on VTE risk and comparison of VTE risk in various cancer patients in our environment.

The objective of this study is to compare the thrombotic risks associated with breast cancer and apparently normal individuals using the modified Khorana risk tool and a biomarker, soluble P-selectin [14].

Materials and Methods

Study design

This was a comparative cross-sectional study. Thrombotic risk status was evaluated and compared between patients with hematologic and breast cancer, an example of solid organ malignancies.

Study area

The study was carried out at the Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi Anambra State, Nigeria. Nnewi is the second largest city in Anambra state, South Eastern Nigeria. It is a metropolitan city with four indigenous communities namely: Otolo, Umudim, Uruagu and Ichi.

Study population

The target study population consisted of patients with:

a. Solid organ malignancies precisely breast cancers diagnosed using standard diagnostic modality (histopathological examination of tissue biopsies).

b. Apparently healthy subjects from same study environment as the study subjects and who were willing to participate in the study.

Period of study

The study was carried out over duration of about six months.

Inclusion criteria for study subjects

a. Individuals with established breast cancer with or without chemotherapy.

Exclusion criteria

a. Overt bacterial or viral infection within the last 2 weeks.

b. Patients on anticoagulants.

4.7. Sample size determination

Sample size was calculated using the formula for cross-sectional study

$$\text{Number of Participants} = \frac{Z\ 2PQ}{d^2}$$

Where Z is the statistic corresponding to level of confidence, P is expected prevalence, Q is (1–P) and d is precision (corresponding to effect size). Z at 95% confidence interval is 1.96; an effect size of 5% will be used for this study. Using the incidence rate 6.5% for VTE estimated by Caruso et al. in patients with breast cancer, the study sample size with be:

$n = 1.962 \times 0.065 \times 0.935/0.052$

n=94

From our record, averages of 50 patients with breast cancer are seen annually. Using the formula for adjusting sample size:

$$nf = \frac{94}{\left(1+\frac{94}{50}\right)}$$

Calculated minimum sample size was 33. However, a total of 45 subjects with breast cancer and 20 controls were recruited.

Sampling technique

Study subjects who satisfied the inclusion criteria were consecutively recruited in the study.

Data collection

Relevant details of study subjects' sex, age (approximated to their nearest birthday), a brief drug history, history of any thrombotic complication, family history and past medical history, tumor stage, level of immobility and history of comorbidities were obtained with a study proforma. Each participant was physically examined and weighed on light clothing using portable way master weighing scale (with a sensitivity of 50 gm) and height in meters determined, Body Mass Index (BMI) was calculated using the standard formula:

Weight (kg)/Height $(m)^2$

Sample collection and processing

Seven (7) ml of venous blood samples were drawn from the antecubital veins after thorough cleaning with antiseptic agent. Of this, 5 ml was dispensed into plasma vacuum tubes (Vacuette®; Greiner Bio-One) containing 1/10 volume, which amounted to 0.5 ml of sodium citrate stock solution (0.129 mmol/L). Citrated Platelet-poor plasma was obtained by centrifuging citrated blood at 1,500 g for 15 min and platelet-free plasma obtained with a 2nd centrifugation step (Eppendorf) at 13,400 g for 2 min. Each sample was centrifuged at 3000 rpm for the above separations to be achieved within 1 h of blood sample collection and frozen. Plasma aliquots were stored at -80°C until they were assayed in series during the time of analysis. Patients and control samples were treated the same. The remaining 2 ml was put into EDTA bottle for immediate full blood count with Coulter HMX Hematology Analyzer for hemoglobin, white cell and platelet count estimation. Soluble P-selectin was measured by means of a highly sensitive sandwich ELISA technique and a commercially available test reagent set (Human soluble P-selectin/CD62P ELISA; R&D Systems) according to the manufacturer's instructions.

Modified Khorana scoring system

The modified Khorana Score (KS) is widely used for the prediction of VTEs in malignancy. This is composed of 5 items including presence of cancer, platelet count >350,000/µL, White Blood Cell Count (WCC) >11,000/µL, Hb <100 g/L and Body Mass Index >35 (BMI). Each parameter is scored 1 when present and 0 if absent. The net score is categorized into 3 risk categories. Net score of 0 imply low risk, 1-2, intermediate risk and 3 or more points, high-risk.

Ethical considerations

Ethical approval was obtained from the Ethics Committee of Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi. The study was conducted within the safe limits of objectivity, integrity, respect, and comfort for the subjects used in the study. Written informed consent was obtained from all participants before the commencement of the study.

Statistical analysis

Data was analyzed with IBM SPSS version 23. Results of categorical variables were presented in simple frequencies while continuous variables were summarized using descriptive statistics. Categorical variables were compared between the groups using Chi-square statistics and continuous variables with student t-test and Analysis of Variation (ANOVA). Statistical significance was set at 0.05.

Results

Sociodemographic parameters of study population

A total of 65 individuals participated in the study. They comprised 45 individuals with Breast Cancer (BRCA) and 20 age and sex matched controls.

The age of individuals with breast cancer ranged from 30 to 74 years with a mean and standard deviation of 46.8 ± 11.4 years while the controls had an age range of 31 to 69 years with a mean and standard deviation of 47.7 ± 11.1 years. The differences in mean was not statistically significant (p=0.774), Table 1.

Fourteen (31.1%) breast cancer patients and 1 (5.0%) control were single, 21 (46.7%) of breast cancer patients and 18 (90.0%) of controls were married while 10 (22.2%) with breast cancer and 1 (5.0%) control were widowed/divorced. There was a statistically significant difference in marital status of the study populace (p=0.012).

Nine (20.0%), 18 (40.0%) and 18 (40.0%) of the subjects with breast cancer had primary, secondary and tertiary educations respectively while in the controls, 1 (5.0%), 15 (75.0%) and 4 (20.0%) of the controls had primary, secondary and tertiary educations respectively. The difference in proportion was not statistically significant (p=0.061).

Duration of illness

Figure 1 is a bar chart showing duration of illness in the BRCA study population. Twenty-nine (64.4%) individuals with breast cancer had been ill for a duration of a year and below while 4 (8.9%) had been ill for a period of 3 years and above.

Co morbidity and social life

Fourteen (31.1%) of BRCA individuals had hypertension and 4

Table 1: Age, anthropometric and blood counts of the study population.

	BRCA n=45 Mean ± SD Range	Controls n=20 Mean ± SD Range	T test	p-value
Age (yrs.)	46.8 ± 11.4	49.6 ± 11.1	0.634	0.774
	30.0-74.0	27.0-72.0		
Weight (Kg/m²)	70.6 ± 16.2	68.0 ± 8.8	1.728	0.496
	45.0-125.0	45.0-95.0		
Height (m²)	1.67 ± 0.12	1.473 ± 0.15	3.121	0.001
	1.45-1.99	1.20-1.74		
BMI (Kg/m²)	25.5 ± 6.6	32.5 ± 7.6	-1.438	0.001
	17.6-46.5	15.9-47.2		
Hemoglobin (g/dL)	11.3 ± 1.8	13.5 ± 2.4	-2.826	0.001
	6.8-14.8	10.2-18.2		
WBC (× 10^9/L)	6.2 ± 3.6	5.8 ± 2.9	1.193	0.642
	1.7-16.8	3.4-13.2		
Platelet (× 10^9/L)	250.5 ± 101.6	247.2 ± 57.8	-2.333	0.001
	70.0-350.0	176.0-375.0		

Table 2: Elements of Khorana score.

	BRCA	Controls	Stats	p-value
BMI >35 Kg/m^2	3 (6.7)	7 (35.0)	Fishers Exact	0.007
Anemia	7 (15.6)	0 (0.0)	Fishers Exact	0.090
Leucocytosis	4 (8.9)	1 (5.0)	Fishers Exact	1.000
Thrombocytosis	3 (6.7)	2 (4.4)	Fishers Exact	0.639

Table 3: Khorana score and risk category.

	BRCA	Controls	Statistical test	P-value
Risk score				
Median	1.0	0.0	Mann Whitney U	0.001
IQR	1.0-2.0	0.0-1.0		
Risk categories				
Low	0 (0.0)	11 (55.0)		
Intermediate	44 (97.8)	9 (45.0)	Fishers Exact	0
High	1 (2.2)	0 (0.0)		

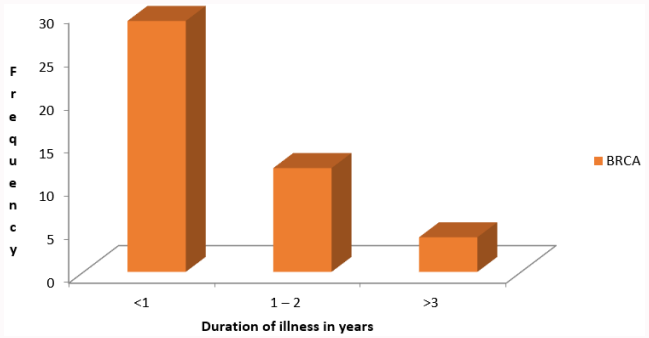

Figure 1: Duration of illness of study subjects.

(8.9%) were diabetic. There was a positive history of alcohol use in 18 (40.0%) individuals.

Treatment history

Sixteen (35.6%) individuals with BRCA had surgeries and 30 (66.7%) were on chemotherapy. Eight (17.8%) individuals had received between 4 to 8 cycles of chemotherapy. While 8 (17.8%) each had received less than 4 cycles and above 8 cycles respectively.

VTE related symptoms

Eleven individuals (24.4%) reported unilateral leg swelling. Similarly, 11 (24.4%) had chest pain. Two (4.4%) had Deep Vein Thrombosis (DVT) based on Doppler scan.

Anthropometrics

Table 1 shows the mean, standard deviation and ranges of weight, height and Body Mass Index (BMI) of the study individuals. The individuals with BRCA had a mean weight of 70.6 ± 16.2 kg while the controls had a mean of 68.0 ± 8.8 kg. There was no significant difference in their mean weight (p=0.468).

The height ranged from 1.4 to 1.99 m in the BRCA individuals was 1.67 ± 0.12 m and the controls (1.47 ± 0.15 m). There was a statistically significant difference in their height (p=0.001).

The mean BMI of the BRCA group was 25.5 ± 6.6 kg/m^2 and the controls had a mean of 32.50 ± 7.8 kg/m^2. The difference in mean BMI was statistically significant (p=0.001).

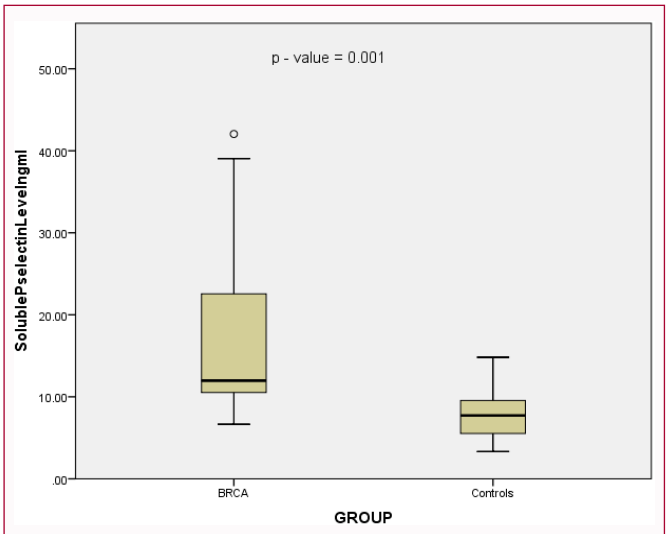

Figure 2: Distribution of soluble P selectin in study population.

Blood count parameters

The mean hemoglobin levels of individuals with the breast cancer 11.3 ± 1.8 g/dl and the controls 13.5 ± 2.4 g/dl. The difference in mean hemoglobin between BRCA individuals and the controls was statistically significant (p=0.89101) Table 1.

The mean white blood cell counts of the BRCA individuals and controls were 6.2 ± 3.6 × 10^9/l and 5.8 ± 2.9 × 10^9/l respectively. The difference in mean WBC was not statistically significant (p=0.642).

The mean platelet counts of the BRCA individuals and controls were 250.5 ± 101.6 × 10^9/l, and 247.2 ± 57.8 × 10^9/l respectively. The difference in mean was not statistically significant (p=0.891), Table 1.

Elements of Khorana score

BMI (Body Mass Index): Three (6.7%) individuals with breast cancer and 7 (35.0%) controls had BMI >35 Kg/m^2. The difference in proportion was statistically significant (p=0.007).

Anemia: Seven (15.6%) individuals with breast cancer and none of the controls had anemia. The incidence of anemia was not significantly different between BRCA individuals and the controls (p=0.090).

Leukocytosis: Four (8.9%) individuals with breast cancer and 1 (5.0%) of the controls had leukocytosis. The difference in the incidence of leukocytosis did not differ significantly between them (p=1.000).

Thrombocytosis: Three (6.7%) individuals with BRCA and 2 (10.0%) controls had thrombocytosis. There was no difference in the incidence of thrombocytosis was not statistically significant (p=0.639) (Table 2).

Modified Khorana risk score

Absolute score: The median (interquartile range) Modified Khorana risk assessment scores of individuals with BRCA and controls were 1.0 (1.0-2.0) and .0 (0.0-1.0) respectively. The difference in median was statistically significant (p=0.000).

Risk category: Forty-four (97.8%) individuals with BRCA had intermediate risk score and 1 (2.2%) had high risk score while 9 (45.0%) of the controls were intermediate risk and 11 (55.0%) low risk. The difference in proportion of risk category was statistically

significant (p=0.000) (Table 3).

P-selectin: The median (IQR) levels of soluble P-selectin in individuals with BRCA and controls were 12.0 (10.1-23.9) ng/mL and 7.7 (5.5-9.6) ng/mL respectively. There was a statistically significant difference in the median (p=0.001), Figure 2.

Discussion

Venous thromboembolism has been a major concern in the management of patients with cancer hence the application of risk assessment scores such as the modified Khorana score to identify at risk patients for appropriate thromboprophylaxis. There is paucity of studies in Nigeria on cancer associated thrombosis hence this study was designed to compare thrombotic risk and incidence of thrombosis in patients with solid organ cancer (breast) and control subjects [15-19]. The subjects with breast cancers were all females understandably because breast cancer is predominantly a female cancer and rarely occurs in males [18-33].

There was a statistically significant difference in the median Interquartile Range (IQR) levels of soluble P-selectin in individuals with Breast Cancer (BRCA) and controls. This is consistent with the study by Dymicka et al. which showed high plasma level of soluble P selectin among colorectal cancer patients [34-35]. In this group of patients, sP-selectin concentration was statistically significantly higher as compared to healthy subjects, irrespective of malignancy grade.

The Cancer Associated Thrombosis (CAT) risk assessment tool used in the study (Modified Khorana scoring system) showed that subjects with breast cancer had significantly increased risk of thrombosis compared to controls. This is consistent with studies by Uduebor and Nwogoh [36] Anna [1] and Heit [2], Jorge et al. [23] and others who reported significantly elevated Khorana score in cancer patients compared to controls and have recommended the use of Khorana score as a predictive risk assessment model for VTE in cancer patients [23]. Thrombotic risk assessment scores have therefore been widely adopted in recommending prophylaxis in cancer patients.

References

1. Anna F. The cancer-thrombosis connection. Hematologist. 2011;8(4).
2. 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. Arch Intern Med. 2000;160(6):809-15.
3. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. Cancer. 2007;110(10):2339-46.
4. Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and predictors of venous thromboembolism among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. Cancer. 2013;119(3):648-55.
5. Sotunmbi PT, Idowu AT, Akang EE, Aken'Ova YA. Prevalence of venous thromboembolism at post-mortem in an African population: A cause for concern. African J Med Sci. 2006;35(3):345-8.
6. Danwang C, Temgoua MN, Agbor VN, Tankeu AT, Noubiap JJ. Epidemiology of venous thromboembolism in Africa: A systematic review. J Thromb Haemost. 2017;15(9):1770-81.
7. Rickles FR, Falanga A. Activation of clotting factors in cancer. Cancer Treat Res. 2009;148.
8. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005;293(6):715-22.
9. Buller HR, van Doormaal FF, van Sluis GL, Kamphuisen PW. Cancer and thrombosis: from molecular mechanisms to clinical presentations. J Thromb Haemost. 2007;5(Suppl 1):246-54.
10. Chen M, Geng JG. P-selectin mediates adhesion of leukocytes, platelets, and cancer cells in inflammation, thrombosis, and cancer growth and metastasis. Arch Immunol Ther Exp (Warsz). 2006;54(2):75-84.
11. Cihan A, Ralph S, Rainer V, Daniela D, Guelay A, Silvia K, et al. High plasma levels of soluble P-selectin are predictive of venous thromboembolism in cancer patients: Results from the Vienna Cancer and Thrombosis Study (CATS). Blood. 2008;112(7):2703-8.
12. A C, Jungbauer LV, Sailer T. High concentrations of soluble P-selectin are associated with risk of venous thromboembolism and the P-selectin Thr715 variant. Clin Chem. 2007;53:1235-43.
13. Massimo F. Thromboembolic risk in hematological malignancies. Clin Chem Lab Med. 2015;53(8):1139-47.
14. Boyle P, Levin B. International agency for research on cancer. World Cancer Report 2008. Lyon, France. 2008.
15. Victor AH, Paul AH. Thrombosis 1, Pathogenesis and Diagnosis. In: Hoffbrand's Essential Haematology; 7th Ed; UK; Wiley Blackwell; 2016.
16. Falanga A, Marchetti M, Vignoli A, Balducci D. Clotting mechanisms and cancer: Implications in thrombus formation and tumor progression. Clin Adv Hematol Oncol. 2003;1(11):673-8.
17. Gary R, Russell H, Harry B. Venous thrombosis. Williams Haematology. 9th Ed; 2016.
18. Thomas GD. Epidemiology and management of uncomplicated thrombosis in cancer patients. Endovascular Today. 2015.
19. Beverley JH, Michael G. Acquired venous thrombosis. In: Post Graduate Haematology; 6th Ed; Wiley Blackwell UK. 2011:888-9.
20. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Oxford Vascular Study. Lancet. 2004;363(9425):1925-33.
21. Klatsky AL, Armstrong MA, Poggi J. Risk of pulmonary embolism and/or deep venous thrombosis in Asian-Americans. Am J Cardiol. 2000;85(11):1334-7.
22. John AH. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015; 12(8):464-74.
23. Jorge D, Martin F, Aristotelis B, Ugo DG, Joaquim B, Lauren CH, et al. The Khorana score in predicting venous thromboembolism for metastatic urothelial carcinoma and variant histology patients treated with chemotherapy. Clin Appl Thromb Hemost. 2017;23(7):755-60.
24. Anna F. The cancer-thrombosis connection; American Society of Haematology self-assessment program. 2011;8(4).
25. Khorana AA. Cancer-associated thrombosis: Updates and controversies. Hematology Am Soc Hematol Educ Program. 2012;2012:626-30.
26. Esmon CT. Basic mechanisms and pathogenesis of venous thrombosis. Blood Rev. 2009;23(5):225-9.
27. Peter LG. Venous thromboembolism. New Eng J Med. 2008;6:358(10):1037-52.
28. Engbers MJ, Van Hylckama Vlieg A, Rosendaal F. Venous thrombosis in the elderly: Incidence, risk factors, and risk groups. J Thromb Haemost. 2010;8(10):2105-12.
29. Joanna LS, Annachiara M, Garth WT, Todd H, Parag M, Owen JT. Platelet count as a predictor of metastasis and venous thromboembolism in

patients with cancer. Converg Sci Phys Oncol. 2017;3(2):023001.

30. Polgar J, Matuskova J, Wagner DD. The P-selectin, tissue factor, coagulation triad. J Thromb Haemost. 2005;3(8):1590-6.

31. Celi A, Pellegrini G, Lorenzet R. P-selectin induces the expression of tissue factor on monocytes. Proc Natl Acad Sci U S A. 1994;91(19):8767-71.

32. Andre P, Hartwell D, Hrachovinova I, Saffaripour S, Wagner DD. Pro-coagulant state resulting from high levels of soluble P-selectin in blood. Proc Natl Acad Sci U S A. 2000;97(25):13835-40.

33. Cihan A, Lea VJ, Thomas S, TheresT, Silvia K, Alexandra K, et al. High concentrations of soluble P-selectin are associated with risk of venous thromboembolism and the P-selectin Thr715 variant. Blood. 2008;112(7):2703-8.

34. Dymicka-P, Butkiewicz A, Matowicka-Karna J, Kemona H. Soluble P-selectin concentration in patients with colorectal cancer. Neoplasma. 2005;52(4):297-301.

35. Blann A, Gurney D, Wadley M, Bareford D, Stonelake P, Lip G. Increased soluble P-selectin in patients with haematological and breast cancer: A comparison with fibrinogen, plasminogen activator inhibitor and von Willebrand factor. Blood Coagul Fibrinolysis. 2001;12(1):43-50.

36. Juliet IU, Benedict N. Thrombotic risk assessment in adult patients with lymphoid malignancies in Benin city: A cross sectional study. Highland Med Res J. 2020;20(1).