

Stratification of the Risk of Venous Thromboembolic Disease in a Cameroonian Group of Patients Diagnosed for Cancer and before Initiating Chemotherapy

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Abstract

Introduction: Cancer increases the risk of venous thromboembolic disease. **Objective:** To assess the level of risk of VTE in a group of Cameroonian cancer patients, before the initiation of chemotherapy, using the Khorana score. **Materials and Methods:** This was an analytical cross-sectional study, with prospective data collection, over 3 months. Including, patients with histopathological evidence of cancer without a history of venous thromboembolic disease, anticoagulant treatment, or chemotherapy. **Results:** Of the 70 patients retained, 53 were women (75.7%). The average age was 46.54 +/- 14.46 years. The main factors predisposing to venous thromboembolic disease were obesity (18.6%), arterial hypertension (15.7%), history of hospitalization (14.3%), and HIV infection (12.9%). The most common cancers were: gynecological-mammary (42.8%), head and neck (18.6%), and digestive (12.8%). The stage of cancer was metastatic in 47.1% of cases. The most represented histological type was carcinoma in 84.3% of cases. Following risk stratification by Khorana score, 22 (31.4%) patients were at low risk, 41 (58.6%) at intermediate risk and 7 (10%) at high risk. Gastric cancer would increase the risk of occurrence of venous thromboembolic disease (OR = 46.5; 95% CI = 3.899 - 554.583). **Conclusion:** At the pre-chemotherapy stage, most Cameroonian cancer patients

present an intermediate or high risk of venous thromboembolic disease, without prior thromboprophylaxis. Gastric cancer would be the factor associated with a high risk of venous thromboembolic disease.

Keywords

Venous Thromboembolic Disease, Cancer, Khorana Score, Yaoundé-Cameroon

1. Introduction

Cancer is one of the leading causes of death worldwide, with approximately 6 million deaths estimated in 2012 by the WHO [1]. In 2018, cancer in Africa accounted for 811,228 new cases and 533,877 deaths in the same year [2]. In Cameroon, the incidence of cancer is 20,745 new cases per year; however, 80% of these patients are diagnosed at an advanced stage with high mortality within the first 12 months following diagnosis [3] [4]. One of the causes of this mortality is venous thromboembolic disease (VTE), which has an incidence of approximately 20% in cancer patients and as high as 50% post-mortem [5]. Thus, on the one hand, cancer increases the risk of VTE by 4 to 7 times compared to healthy subjects; and on the other hand, systemic chemotherapy potentiates the risk of VTE in patients who are already predisposed to this complication [6] [7]. Assessing the level of risk of VTE in cancer patients before starting chemotherapy is therefore essential. However, this is not done systematically [8]. Several risk scores for cancer patients have been proposed and validated, including the Khorana score, which is the most widely used [9]. The main objective of our study was to use the Khorana score to assess the level of risk of MTEV in a group of Cameroonian cancer patients before the initiation of chemotherapy and who had not previously received thromboprophylaxis.

2. Methodology

2.1. Type of Study

This was a cross-sectional analytical study conducted in the Cardiology Department of Yaoundé Central Hospital and the Medical Oncology Department of Yaoundé General Hospital in Cameroon within three months from April 1 to June 31, 2021.

2.2. Participants

The study population consisted of cancer patients undergoing outpatient treatment, in the pre-chemotherapy stage and naïve to thromboprophylaxis, who had given their free and informed consent. Using a pre-established and pre-tested data collection form, sociodemographic (age, sex, occupation), clinical (predisposing factors for VTE), histopathological (location, histological type, cancer stage), and

therapeutic data were recorded. Patients with a history or signs of VTE and/or who had already received at least one chemotherapy treatment were excluded. The Khorana score (9) was used to calculate the risk of VTE in this study population. The risk was classified as high risk (score ≥ 3), intermediate risk (score between 1 and 2), and low risk (score = 0).

2.3. Sample Size Estimation

The minimum sample size was estimated at 56 using the Cochrane formula, considering the prevalence of cancer as the etiology of VTE, which is 3.8% according to a study by Abah *et al.* [10] in Cameroon. In our study, we considered a power of 80% with a Z value equal to 1.96.

2.4. Ethical Considerations

The study was conducted in accordance with the principles and standards of the Helsinki Declaration, revised in 2013. Ethical approval was obtained from the Institutional Ethics and Research Committee of the Université des Montagnes (No. 052/UdM/PR/CIE).

2.5. Statistical Analyses

Qualitative variables were expressed as counts and percentages. Quantitative variables were expressed as means and standard deviations after checking the distribution using the normality test. Frequency comparisons were made using the chi-square test or Fischer's test in cases where the cell count was less than 5. Binary logistic regression was used to identify factors associated with a high risk of VTE. We used an error threshold of $\alpha = 5\%$. Statistical analyses were performed using SPSS 20 software.

3. Results

Of the 435 patients invited to participate in the study, 362 were excluded due to chemotherapy initiation, 3 due to a history of VTE and anticoagulant treatment. The flow chart of study participants (patients) is shown in **Figure 1**. We selected 70 participants, including 27 men (24.3%) and 53 women (73.7%), representing a female-to-male ratio of 3. The average age of our study population was 46.54 \pm 14.46 years (ranging from 16 to 83 years). The most represented professional sector was the informal sector (31.4%), and 85.7% of subjects did not have health insurance.

The main factors predisposing to VTE were obesity (18.6%), arterial hypertension (15.7%), a recent history of hospitalization (14.3%), and HIV infection (12.9%).

Gynecological and breast cancers were the most common, accounting for 30 (42.8%) cases, including 20 (28.6%) cases of breast cancer. These were followed by head and neck cancers (18.6%) and digestive cancers (12.8%). The main histological type was carcinoma, and all cancers were at the metastatic stage in 47.1%

of cases. (See **Table 1**). After estimating the risk of VTE according to the Khorana score, 7 patients (10%) were at high risk (score ≥ 3); 41 (58.2%) were at intermediate risk (score between 1 and 2), and 22 (31.4%) were at low risk (score = 0). (See **Table 2**). The indication for thromboprophylaxis represented by intermediate and high levels accounted for 68.2%. After bivariate analyses taking into account gender, modifiable cardiovascular risk factors, cancer type, location, and extent, only gastric cancer was significantly associated with the risk of VTE. (See **Table 3**).

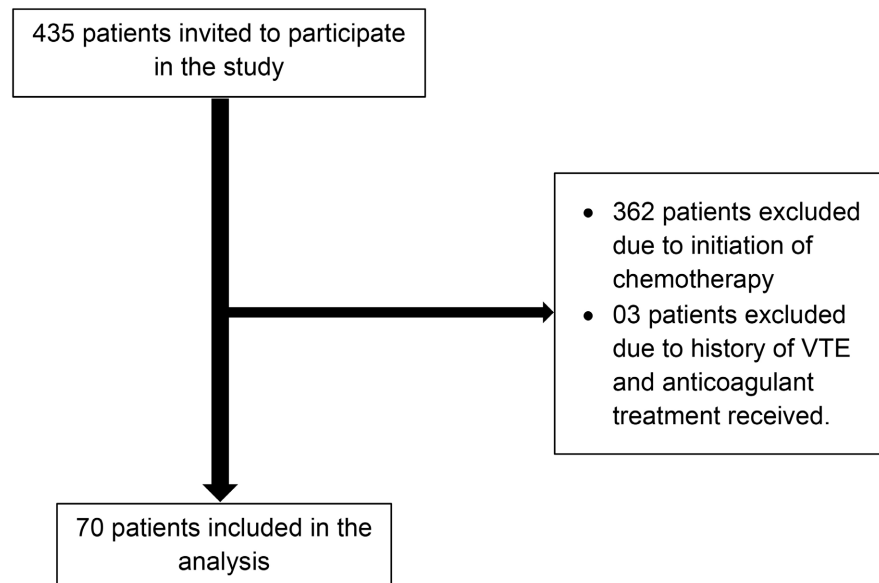


Figure 1. Flow chart of study participants.

Table 1. Predisposing factors for VTE and histopathological characteristics of the study population.

Variables	Counts (N = 70)	Percentages (%)
Obesity (BMI > 30 kg/m²)	13	18.6
High blood pressure	11	15.7
Surgery		
Major abdominal	3	4.3
Breast surgery	2	2.9
Other*	2	2.9
HIV infection	9	12.9
Supportive treatment		
Erythropoiesis-stimulating agents	3	4.3
Red blood cell concentrate	7	10.0

Continued

Diabetes	7	10.0
Recent hospitalization	10	14.3
Cancer site		
Breast cancer	20	28.5
Cervical cancer	2	2.8
Ovarian cancer	4	5.7
Uterine cancer	1	1.4
Head and neck cancers	14	20
Gastric cancer	4	12.8
Pancreatic cancer	1	1.4
Colon cancer	4	5.7
Lung cancer	5	7.1
Prostate cancer	5	7.1
Kidney cancer	1	1.4
Bladder cancer	1	1.4
Hematologic malignancy	4	5.7
Other	4	5.7
AJCC classification		
Metastatic	33	47.1
Locoregional	25	35.7
Localized	6	8.6
Locally advanced	6	8.6
Histological type		
Carcinoma	59	84.3
Sarcoma	5	7.1
Lymphoma	5	7.1
Blastoma	1	1.4

VTE: Venous Thromboembolic Event; BMI: Body Mass Index; HIV: Human Immunodeficiency Virus; AJCC: American Joint Committee on Cancer.

Table 2. Assessment of VTE risk according to the Khorana score.

Variables	Counts (N = 65)	Percentages (%)
Cancer site		
Very high-risk sites (stomach, pancreas)	5	7.7
High-risk sites (lung, lymphoma, gynecological, bladder, kidney)	21	32.3
Platelet count (>350 G/l)	21	32.3
Hemoglobin level (<10 G/l)	5	7.7
Leukocyte count (>11 G/l)	9	13.8
BMI \geq 35 kg/m²	4	6.1
Overall risk assessment		
High risk (score \geq 3)	7	10
Intermediate risk (score [1-2])	41	58.6
Low risk (score = 0)	22	31.4

VTE: Venous Thromboembolic Event; BMI: Body Mass Index.

Table 3. Factors associated with high risk of VTE according to the Khorana score.

Variables	High risk		OR (95% CI)	p-value
	Yes	No		
Gender				
Male	2(11.7)	15 (88.3)	1.28 (0.225 - 7.287)	0.780
Female	5(9.4)	48 (90.5)		
Obesity				
Yes	0	13 (100)	/	0.334
No	7 (12.3)	50 (87.7)		
Diabetes				
Yes	0	7 (100)	/	1,000
No	7 (11.1)	56 (89.9)		
High blood pressure				
Yes	1 (9.1)	10 (90.9)	0.883 (0.096 - 8.151)	1.000
No	6 (10.2)	53 (89.8)		

Continued

HIV infection				
Yes	1 (11.1)	8 (89.9)	1.146 (0.122 - 10.79)	1.000
No	6 (9.8)	55 (90.2)		
Supportive treatment				
Yes	0	10 (100)	/	0.582
No	7 (11.7)	53 (88.3)		
History of hospitalization				
Yes	2 (20)	8 (80)	2.75 (0.455 - 16.632)	0.260
No	5 (8.3)	55 (91.7)		
Pancreatic cancer				
Yes	0	1 (100)	/	0.113
No	7 (10.1)	62 (89.9)		
Gastric cancer				
Yes	3 (75)	1 (25)	46.5 (3.88 - 554.58)	0.002
No	4 (6.1)	62 (93.9)		
Lung cancer				
Yes	1 (20)	4 (80)	2.458 (0.235 - 25.693)	0.419
No	6 (9.2)	59 (90.8)		
Kidney cancer				
Yes	1 (100)	0	/	0.1
No	6 (8.7)	63 (91.3)		
Bladder cancer				
Yes	0	1 (100)	/	1.00
No	7 (10.1)	62 (89.9)		
Ovarian cancer				
Yes	0	4 (100)	/	1.00
No	7 (10.6)	59 (89.4)		
Cervical cancer				
Yes	1 (33.3)	2 (66.7)	5.083 (0.4 - 64.630)	0.275
No	6 (9)	61 (91)		

Continued

Breast cancer				
Yes	0	20 (100)	/	0.18
No	7 (14)	43 (86)		
Local				
Yes	0	6 (100)	/	1.00
No	7 (10.9)	57 (89.1)		
Locally advanced				
Yes	0	6 (100)	/	1.0
No	7 (10.9)	57 (89.1)		
Locoregional				
Yes	1 (4)	24 (96)	0.271 (0.031 - 2.389)	0.408
No	6 (13.3)	39 (86.7)		
Metastatic				
Yes	6 (18.2)	27 (81.8)	8 (0.909 - 70.418)	0.046
No	1 (2.7)	36 (97.3)		
Carcinoma				
Yes	5 (8.5)	54 (91.5)	0.417 (0.07 - 2.484)	
No	2 (18.2)	9 (81.8)		
Sarcoma				
Yes	0	5 (100)	/	
No	7 (10.8)	58 (89.2)		
Lymphoma				
Yes	1 (25)	3 (75)	3.33 (0.298 - 37.253)	
No	6 (9.1)	60 (90.9)		
Nephroblastoma				
Yes	1 (100)	0	/	0.10
No	6 (8.7)	63 (91.3)		

VTE: Venous Thromboembolic Event; OR: Odds Ratio; CI: Confidence Interval.

4. Discussion

Although it is established that cancer increases the risk of venous thromboembolic disease, we set out to assess the level of risk of this condition in patients being

treated for cancer before the start of chemotherapy at the Central Hospital and General Hospital in Yaoundé using the Khorana score. The results show that, at the pre-chemotherapy stage, cancer patients have an intermediate or high risk of developing this condition and that gastric cancer is a factor associated with a high risk of VTE.

4.1. Limitations of the Study

The study we conducted has the advantage of being one of the studies evaluating the risk of VTE in cancer patients in our population. Furthermore, given the ever-increasing morbidity and mortality rates due to VTE in sub-Saharan Africa, this study aims to find an effective and inexpensive alternative in the Khorana Score risk assessment to improve the management of cancer patients in the pre-chemotherapy stage. However, this study has some limitations that should be noted: the small sample size and the study sites (two hospitals, although they are referral hospitals) do not allow for good representation of all types of cancer. Furthermore, the cross-sectional nature of the study does not allow for an assessment of the incidence of VTE after risk assessment in this group of subjects.

4.2. Characteristics of the Study Population

Our sample consisted of 70 patients, with women being the most represented group, accounting for 53 (75.7%) of the total. The female-to-male ratio was 3. This predominance of women can be explained by the fact that the two most common cancers in Cameroon are breast and cervical cancer, which are specific to women [3]. According to the Yaoundé cancer registry, 61.85% of cancer cases affect women [9]. The average age was 46.54 \pm 14.46 years, which is similar to the average age according to the Yaoundé cancer registry [11].

4.3. Main Risk Factors for VTE

The main risk factors for VTE in cancer patients were obesity (18.6%), high blood pressure (15.7%), recent hospitalization (14.3%), and HIV infection (12.9%). This result is similar to that of Etoundi *et al.* in their study at the Yaoundé Central Hospital, which reported that obesity and high blood pressure were the main risk factors, at 30.23% and 25.58%, respectively [12]. These data are once again consistent with the study by Kamdem *et al.* in a retrospective study over a 6-year period at the General Hospital of Douala, Cameroon, which also found obesity (44.9%) and high blood pressure (37.2%) to be the main risk factors [13].

4.4. Clinical Characteristics of Cancers

The distribution of the population according to cancer location was as follows: 20 breast cancers, 14 head and neck cancers, 5 lung cancers, 5 prostate cancers, 4 gastric cancers, 4 colon cancers, 4 ovarian cancers, 4 malignant blood disorders, 2 cervical cancers, and cancers of the pancreas, bladder, and kidney, each with a proportion of 1.

The metastatic stage was the most common, with a percentage of 47.1%. This result is similar to that obtained in a previous study at the Yaoundé General Hospital, where 60% of cancer patients arrive at an advanced stage [11]. The most common histological type was carcinoma, with a percentage of 84.3%. This result could be explained by the predominance of breast cancer in the study population, given that the most common histological type of breast cancer is adenocarcinoma, accounting for 96.5% of cases.

4.5. Factors Associated with High Risk of VTE

After assessing risk using the Khorana score, we found that 7 patients were at high risk of VTE, 41 were at intermediate risk, and 22 were at low risk. We found no significant association between obesity, high blood pressure, and high risk of VTE, contrary to data from systematic reviews on VTE in cancer [14]. Based on location, only gastric cancer is significantly associated with a high risk of VTE, consistent with studies that classify it among the most thrombogenic neoplasms [14]-[16]. Pancreatic cancer was not significantly associated with a high risk of VTE, contrary to the study by Kpossou *et al.* in Benin on a population of patients monitored for digestive cancer, which found that pancreatic cancer was the neoplasm most likely to cause VTE [17]. This difference can be explained by the low number of pancreatic cancers in our population, as the majority of patients approached were already undergoing chemotherapy, given that diagnosis is most often made late at an advanced stage. Breast cancer, which is common in our population, is not associated with high risk, which is similar to data in the literature that classify breast cancer as one of the cancers with a low risk of VTE [18]. Studies that report a higher incidence of VTE in breast cancer patients have been conducted in patients already undergoing chemotherapy [19], thus overestimating the risk. The lack of association with other factors (obesity, hypertension, extension) can be explained by the low number of high-risk patients [7], due to a Khorana score threshold set at ≥ 3 . Thus, there is a proportion of patients who fall into the intermediate risk category, which makes its clinical applicability suboptimal, as suggested by recent randomized trials that have adopted the use of a threshold of ≥ 2 to stratify cancer patients who are candidates for thromboprophylaxis. The feasibility of a revised threshold of ≥ 2 points was recently confirmed in a meta-analysis specifically designed to estimate the performance of the Khorana score. Using a threshold of 2 points rather than the conventional 3 points, there was a substantial increase in the proportion of high-risk patients (from 17% to 47%), along with a reduction in the absolute risk of VTE from 11% to 9% (20).

5. Conclusion

The assessment of the risk of venous thromboembolic disease in cancer patients prior to chemotherapy should be systematic, as should the initiation of thromboprophylaxis before the start of chemotherapy. Our study suggests an association between gastric cancer and a high risk of VTE. It would be important to intensify

efforts to combat the predisposing factors for this condition, particularly in this specific population.

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Authors' Contributions

CNNG, EAO, and IFFN designed the study; CNNG, EAO, PC, EM, BH and FK supervised data collection; IFFN and FMNN collected and analyzed the data; IFFN and ATTT drafted the manuscript; CNNG, EM, BL, PT and BH made substantial revisions to the manuscript; all authors read and approved the final manuscript.

Availability of Data and Materials

The data collected during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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