

# Venous thromboembolism among gynecologic cancer patients in Zaria

Hauwa Sanusi Gumbi,<sup>1</sup> Anisah Yahya,<sup>1</sup> Musliu Tolani,<sup>2</sup> Marliyya Zayyan,<sup>1</sup> Aisha Mustapha,<sup>1</sup> Abimbola Omolara Kolawole,<sup>1</sup> Sunday Adewuyi,<sup>3</sup> Adekunle Oguntayo<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynaecology, <sup>2</sup>Department of Urology, <sup>3</sup>Department of Radiotherapy/Oncology, Ahmadu Bello University Teaching Hospital, Zaria, Nigeria

## Abstract

Cancer is one of the most important acquired risk factors for Venous Thromboembolism (VTE) including Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE). Patients with active malignancy have up to six-fold increased risk of symptomatic VTE than the general population. The risk of VTE in patients with gynecologic malignancy is especially high because of the nature of the tumor, its pelvic location, associated comor-

bidities, and systemic chemotherapy. The objective of this study was to determine other risk factors, incidence, clinical presentation, and immediate outcome of treatment of thromboembolism in patients with gynecologic cancers in Ahmadu Bello University Teaching Hospital (ABUTH), Zaria, Nigeria. It was a retrospective cross-sectional descriptive study of gynecologic cancer cases that were diagnosed with VTE while on admission from 2007-2016 in ABUTH. The overall prevalence of clinical VTE was 2.8% in gynaecologic malignancy. All were DVT. Most cases of DVT were present in ovarian cancers with left-sided preponderance. There is a need for the provision of modern imaging equipment to facilitate timely and highly sensitive diagnosis of VTE in low-resource settings. The main limitation of this study was the inability to find any confirmed case of PE.

Correspondence: Aisha Mustapha, Department of Obstetrics and Gynaecology, Ahmadu Bello University Teaching Hospital, Zaria, Nigeria. Tel. +2348035832139.  
E-mail: aisha.mustapha@nmpcn.edu.ng

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## Introduction

Gynecologic cancers are established causes of Venous Thromboembolism (VTE) including Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE). Patients with active malignant disease have about a six-fold increased<sup>1</sup> risk of VTE due to the Virchow triad of hypercoagulability, stasis, and epithelial injury. Gynecologic cancer patients have the highest risk of VTE among all malignancies.<sup>1</sup> VTE is the second cause of death in gynecologic cancer patients, with the highest incidence associated with ovarian cancer. The increased risk of VTE in cancer patients is due to the complex interplay of the patient, disease, and treatment-related factors.<sup>2</sup>

The epidemiology of patients commonly affected by gynecologic cancers further increases their risk. Age of greater than 40 years, varicose veins, obesity, being bedridden for more than 48 hours, surgery for more than 3 hours, and histologic diagnosis of adenocarcinoma further increase their risk. Co-morbidities, which are often associated with malignant conditions like secondary renal insufficiency or disease are independent contributory factors.<sup>3</sup> Furthermore, treatment by extensive oncologic surgery, prolonged hospital stay, chemotherapy, and radiotherapy increase the risk of VTE manyfold.<sup>4,5</sup> The development of VTE in cancer patients worsens their prognosis.<sup>5</sup>

Several prophylactic measures are being used to curtail thrombosis including graded compression stockings, intermittent pneumatic compression devices, inferior vena cava filters, and/or pharmacologic agents.<sup>5,6</sup>

Diagnosis of VTE based on clinical signs is accurate in only 25% of cases because the symptoms and signs are neither sensitive nor specific. Most of the clinical features are often non-specific or mimic the underlying disease condition.<sup>7</sup>

Asymptomatic VTE is not uncommon, especially in pelvic veins, and clinical diagnosis is based on the demonstration of pitting edema on the affected side and calf circumference measurement at 10 cm below tibial tuberosity of 3 cm or greater from the unaffected leg (the normal difference is less than 1 cm).<sup>7</sup>

Abdominal pain may be the presenting symptom in patients with thrombosis in the pelvic veins. This is often considered to be due to her primary disease.<sup>2</sup>

Classical symptoms of DVT are pain, redness in the affected leg, and unilateral edema with or without a positive Homan sign are typical of DVT, and measures are required to confirm the diagnosis. However, the commencement of treatment is mandatory with high clinical suspicion while measures are taken to confirm the diagnosis.<sup>2</sup>

Arterial Blood Gases (ABG) will reveal hypoxia, and acidosis as well as a ventilation-perfusion mismatch, B-mode Duplex Doppler ultrasound can reliably show a lack of vein wall compressibility but is limited by the inability to perform maneuvers (that will demonstrate this criterion above the inguinal ligament). Contrast venography is the gold standard and the demonstration of an intraluminal filling defect in at least two different projections is a reliable diagnostic criterion. Magnetic resonance venography, though as accurate as duplex USS, is limited by cost.<sup>8</sup> Elevated levels of fibrin mesh breakdown products could be seen on D-dimer tests but this has a high negative predictive value and thus cannot be relied on alone. However, lack of D-dimer elevation in combination with a negative non-invasive imaging test reliably excludes lower extremity DVT.<sup>6,9</sup>

Pulmonary embolism presents with pleuritic chest pain, hemoptysis, dyspnea, tachycardia, and tachypnoea. Ventilation-Perfusion (V-Q) scan is the gold standard for confirming the diagnosis. Chest Computerized Tomography (CT) scan and CT pulmonary angiography are also very sensitive; the former may be more readily available while the latter is invasive and requires an interventional radiologist. Other investigations like chest X-ray, electrocardiogram, and echocardiography could be supportive or relied upon where a V-Q scan is not available.<sup>6</sup>

Prediction and screening for VTE in gynecologic oncology patients are backed by good clinical evidence. A systematic review of eleven studies that combined the Wells prediction rule with the D- D-dimer assay found that patients with a low pretest probability and a negative D-dimer assay had a 3-month incidence of DVT of 0.5% as opposed to DVT incidence of 21.4% in those with negative D-dimer test and high pretest probability.<sup>9</sup> This practice keeps physicians on guard about patients at high risk and may pick early events.

The American Society for Hematologists (ASH) recommends the use of directly acting oral anticoagulants as first line for treatment of acute PE or DVT anticoagulation therapy alone is preferred over thrombolytic therapy for proximal DVT.<sup>10</sup> Thrombolysis is usually considered in patients presenting with limb-threatening DVT (phlegmasia cerulea dolens) or in carefully selected younger patients with ilio-femoral DVT at low risk of bleeding.<sup>10</sup>

Despite advances in its prevention and management, VTE remains a common and often unrecognized cause of morbidity and mortality.<sup>11</sup>

The lack of guidelines for diagnosis and treatment, the need for multidisciplinary care and the additional cost of investigations and treatment further worsen the plight of patients with thromboembolic disease in our setting. The purpose of this study was to explore other risk factors for thromboembolism, the clinical presentation, and outcome of gynecologic cancer patients with VTE over a period of 10 years in Ahmadu Bello University Teaching Hospital, Zaria, Nigeria.

Results from this study will provide insight into the commonly associated risk factors in our patients which could enhance our awareness and pro-action.

## Materials and Methods

It was a retrospective cross-sectional descriptive study of gynecologic cancer cases admitted into the gynecology and radio-oncology wards via accident and emergency unit and those seen in gynecological and radio-oncology clinics diagnosed with thromboembolism over ten years (January 1 2007 to December 31 2016).

The total number of patients managed for gynecologic cancer over the ten years was retrieved from the gynecology and radio-oncology records department for the study period. Using the hospital numbers, folders were traced from the gynecology clinic records unit, the radio-oncology records unit, and the central library of hospital records. Folders of patients diagnosed with VTE were selected. Patients with gynecologic cancer in pregnancy and case notes with incomplete information were excluded from the study.

Sociodemographic details, type of cancer with VTE, site of thromboembolism, duration of hospital stay, and details of management were obtained from the folders were extracted and filled into a predesigned proforma. Data was analyzed using the Statistical Package for Social Sciences (SPSS) software version 20. Descriptive statistics were used to define continuous variables and frequencies for categorical variables.

Ethical approval was obtained from the Ahmadu Bello University Health Research and Ethical Committee (with code ABUTHZ/HREC/G29/2019).

## Results

During the period under review, a total of 951 gynecologic cancer cases were recorded, however, a total of 725 case folders were retrieved and available for detailed assessment giving a retrieval rate of 76.2% (Table 1).

Comorbidities were present in 70.4 % (19) of the cases. Hypertension was found to be the most prevalent as it was present in 51.9 % (11) cases. Others include Diabetes Mellitus and Immobility.

The duration of the disease among cases ranged from 5 to 24 months with a mean duration of  $10.22 \pm 5.66$  months, while that of Hospital stay ranged from 2 to 86 days with a mean of  $24.89 \pm 24.63$  days. The result is presented in Table 2.

Available data of 725 patients diagnosed with gynecologic cancer (out of 951 cases) within the study duration included: cervical cancer at 65.6%, endometrial cancer at 16.8%, ovarian cancer at 12.4%, and others at 5.2%. A total of 27 patients were diagnosed with clinical VTE giving a prevalence of 2.8%. Clinical VTE was observed mainly in two types of malignancies - cervical and ovarian/fallopian tubes. Of the 27 clinical VTE cases, the majority (59.3%) of them occurred in ovarian cancer patients of the cases as shown in Figure 1.

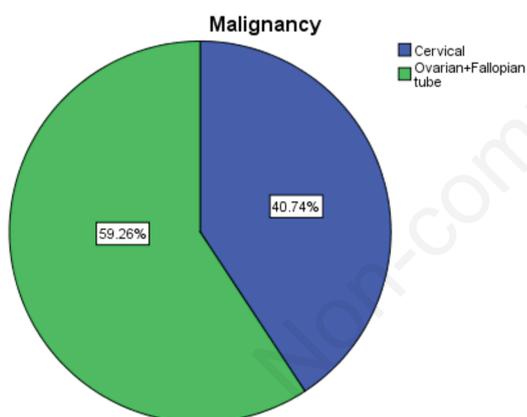
The presenting symptoms of VTE cases were perused and it was observed that 66.6% of the cases presented with Pains in the leg, 81.5 % presented with unilateral swelling, and 7.4% with bilateral swelling. All cases of VTE were diagnosed with DVT. There was a left lower limb preponderance of 66.7% (Figure 2). Most of the cases were diagnosed clinically (88.9%) with a few (11.1 %) diagnosed with both clinical and imaging methods using Doppler ultrasound.

Not all presented cases received treatment as some cases (11.1%) could not afford the prescribed medications (Table 3).

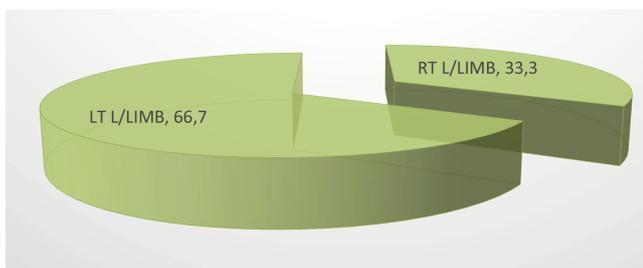
## Discussion

In this study, the prevalence of clinically significant VTE was 2.8%. This is similar to the findings of a hospital study that reported a prevalence of 2.0% over 10 years.<sup>4</sup> All the diagnosed VTE in this study were DVT and no PE was diagnosed. Death from a PE occurs rapidly with most patients succumbing within 30 minutes of the first clinical symptoms, thus inadequate time exists for diagnosis or therapeutic interventions. It is a bit difficult to diagnose PE in our setting due to the unavailability of Computed Tomography Pulmonary Angiography (CTPA), low index of suspicion, and lack of autopsies due to religious reasons. This may explain why no case of PE was documented over the study period.<sup>11</sup> Hence strategies to lower the rate of fatal PE must be directed at preventing the occurrence of DVT.<sup>4</sup> Ovarian cancer patients accounted for 59.26% of VTE in this study. This is in keeping with reports that ovarian cancer has a higher incidence of VTE than other cancers.<sup>10,12,13</sup> All were serous adenocarcinomas similar to Oranratanaphan's findings of higher risk in adenocarcinoma of the ovary.<sup>1</sup> The mean hospital stay in this study was 26 days. Hospitalization and surgery are also associated with an increased thrombosis risk, with odds ratios of 11.1 and 5.9, respectively.<sup>14</sup>

Hypertension (40.7%) was found to be the most common medical comorbidity in this study, followed by immobility (18.5%). Another study similarly reported the incidence of symptomatic VTE as 1.295% over 10 years and hypertension was the most common comorbid condition.<sup>1</sup> Most of the cases were diagnosed clinically (88.9%) with a few (11.1%) diagnosed with both clinical



**Figure 1.** Type of gynecologic malignancy observed among Venous Thromboembolism (VTE) cases.



**Figure 2.** Occurrence of Deep Vein Thrombosis (DVT) by site.

**Table 1.** Socio-demographic characteristics of patients diagnosed with Venous Thromboembolism (VTE).

Socio-demographic variable	Frequency	Percentage (%)
<b>Age (years)</b>		
<41	6	22.2
41-49	9	33.3
50-59	9	33.3
>59	3	11.1
Total	27	100.0
<b>Gender</b>		
Female	27	100.0
Total	100	100.0
<b>Marital status</b>		
Married	21	77.8
Widowed	6	22.2
Total	27	100.0
<b>Marital type</b>		
Polygamous	17	63.0
Monogamous	10	36.4
Total	27	100.0
<b>Tribe</b>		
Hausa	21	77.8
Yoruba	4	14.8
Others	2	7.4
Total	27	100.0
<b>Education</b>		
Primary education	7	25.9
Secondary	14	51.9
Tertiary	6	22.2
Total	27	100.0
<b>Occupation</b>		
Housewife	24	88.9
Trader	3	11.1
Total	27	100.0

**Table 2.** Duration of illness among retrieved Venous Thromboembolism (VTE) cases seen at ABUTH, Zaria (n=27).

Duration	Frequency	Percentage (%)
<b>Disease (months)</b>		
<6	3	11.1
6-12	21	77.8
>12	3	11.1
Total	27	100.0

**Table 3.** Treatment and outcome among reviewed Venous Thromboembolism (VTE) cases seen at ABUTH, Zaria (n=27).

Timing	Frequency	Percentage (%)
<b>Treatment</b>		
Yes	21	77.8
No	6	22.2
Total	27	100.0
<b>Outcome</b>		
Died	18	66.7
Alive	9	33.3
Total	27	100.0
<b>Management</b>		
Radio oncologist	12	44.4
Hematologist	6	22.0
Interventional radiologist	3	11.1
General surgeon	3	11.1
Total	24	88.6

and imaging, by Doppler imaging of the lower limbs. This may be explained by the unavailability of other diagnostic modalities in our setting. Furthermore, most of these patients cannot afford Doppler imaging even when it is requested. Left-sided preponderance (66.7 % vs 33.3 %, ratio 2:1) observed in this study is similar to that reported in a study where lower extremity DVT accounted for 32.6% and there existed a preponderance of left-sided DVT (47.5% vs 17.0%, ratio 2.79:1).<sup>4</sup> The preponderance of left-sided DVT can be attributed to left common iliac vein compression by the right common iliac artery.<sup>15</sup>

Despite multidisciplinary teams being involved in the management of 77.8 % of the cases in this study, 55.6% of the total cases died. Though, further studies would be needed to determine whether the occurrence of DVT was causal, as the cause of death in gynecological cancer patients is multifactorial.

## Conclusions

The overall incidence of clinical VTE was 2.8 % in gynecologic malignancy. Most cases of DVT were present in ovarian cancers with left-sided preponderance. In a resource-poor setting like ours, diagnosis is largely clinical. A third (33.3%) of the patients were alive and discharged.

## Recommendations

There is a need for the provision of modern imaging equipment to facilitate timely and highly sensitive diagnosis of VTE in low-resource settings.

## Limitations

The retrospective nature of the study can limit the level of evidence. There was also no documented case of PE due to non-availability of diagnostic facilities or autopsies.

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