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CLINICAL CHARACTERISTICS AND PROGNOSIS OF PATIENTS WITH CANCER-ASSOCIATED THROMBOSIS

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Abstract

Introduction: Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (BE), is a very common and potentially fatal disease. The incidence of VTE in cancer patients is about 4–7 times higher compared to healthy individuals and appears to increase over time.

Aim: The aim of this study is to evaluate the clinical characteristics and prognosis of patients with cancer-associated thrombosis.

Material and methods: This prospective observational single-center clinical study enrolled 30 patients with active cancer, divided into 3 groups, according to the location of thrombosis: deep vein thrombosis (DVT), pulmonary embolism (PE), and DVT with PE. Clinical characteristics between these three groups and their prognosis were compared.

Results: The study included 20 patients, of whom 9 (45%) were women and 11 (55%) were men, with a mean age of 54 ±13.7 years. The prevalence of risk factors and comorbidities was determined:10 patients had hypertension (50%), 6 patients had chronic kidney disease (30%), 3 patients had diabetes (15%), 2 patients had hepatic lesion (10%). Smoking was observed in 8 patients (40%).Uurogenital carcinoma was predominantly present in 4 patients, with ovarian cancer and 1 patient with cervical uterine carcinoma (25%). In men, prostate cancer was present in 3 patients (15%), while testicular cancer in 1 patient (5%). Kidney cancer had 2 patients (10%). Breast cancer accounted for 15% (3 patients), 3 patients or 15% were with colon cancer and 2 patients or 10% with pancreatic cancer and lung cancer in 1 patient (5%). PTE was diagnosed in 13 patients (65%), DVT alone was detected in 9 patients (45%), and combined DVT with PTE was reported in 2 patients (10%). DOACs were administered as home therapy in 55% (11 patients). 7 patients (35%) were treated with LMWH, and only 4 patients (20%) were prescribed with VKA.

Conclusion: The use of DOACs is an effective and safe treatment option for VTE in selected cancer patients. LMWH remain a treatment option in patients with cancer at high risk of bleeding, such as patients with gastrointestinal and genitourinary cancer, patients with chemotherapy-induced thrombocytopenia, patients receiving anticancer therapies with potential interactions with DOAC and those with brain metastases.

Keywords: venous thromboembolism, cancer, DOAC.

Introduction

Cancer-associated thrombosis (CAT) represents one of the most significant complications in oncology, contributing substantially to morbidity and mortality among patients with malignancies. Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is recognized as the second leading cause of death in cancer patients, following disease progression itself [1,2].

Compared to the general population, patients with cancer have a 4- to 7-fold increased risk of developing VTE [3], with certain malignancies carrying even higher risks depending on tumor type, stage, and treatment modalities.

The association between cancer and thrombosis was first described by Armand Trousseau in the 19th century, highlighting migratory thrombophlebitis as a manifestation of occult malignancy [4].

Since then, extensive research has elucidated the complex and multifactorial mechanisms underlying this relationship. Cancer induces a hypercoagulable state through tumor-related, host-related, and treatment-related mechanisms involving activation of coagulation pathways, platelet activation, endothelial dysfunction, and inflammatory responses [5,6].

Tumor cells play a central role in the pathogenesis of CAT by expressing procoagulant factors such as tissue factor (TF), which activates the extrinsic coagulation pathway [7]. Additionally, tumor-derived microparticles carrying TF contribute to systemic hypercoagulability [8].

Malignant cells also release cytokines and pro-inflammatory mediators that stimulate platelet activation and aggregation, further promoting thrombus formation [5].

Chronic inflammation, a hallmark of malignancy, further enhances thrombotic risk. Elevated levels of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) contribute to coagulation activation and suppression of fibrinolysis [6]. Endothelial injury and dysfunction, often induced by tumor invasion or treatment, also play a key role in thrombogenesis [9].

Risk factors for CAT are multifactorial and can be categorized into patient-related, cancer-related, and treatment-related factors. Patient-related factors include advanced age, immobility, obesity, comorbidities, and thrombophilia [10].

Cancer-related factors include tumor type, stage, and presence of metastases, with pancreatic, gastric, lung, brain, and hematologic malignancies being associated with the highest risk [3,11]. Treatment-related factors include surgery, chemotherapy, hormonal therapy, antiangiogenic agents, and central venous catheters [12].

The incidence of VTE varies significantly across malignancies and clinical settings. Hematologic malignancies, such as lymphoma and multiple myeloma, are associated with an increased risk of thrombosis, particularly in patients receiving immunomodulatory drugs [13]. The risk of VTE is highest during the first months after cancer diagnosis and during active treatment [14].

The clinical impact of CAT is profound. In addition to being potentially fatal, it is associated with increased risk of recurrence, bleeding complications related to anticoagulation, delays in cancer therapy, and reduced quality of life [2,15]. Importantly, the occurrence of VTE is considered an independent predictor of poor prognosis and reduced overall survival in cancer patients [16].

Several risk assessments models have been developed to identify patients at high risk of VTE. The Khorana score is the most widely used and incorporates clinical and laboratory parameters such as tumor type, platelet count, hemoglobin level, leukocyte count, and body mass index [17].

Other models, including the Vienna Cancer and Thrombosis Study (CATS) score and COMPASS-CAT score, aim to improve predictive accuracy by incorporating biomarkers and additional clinical variables [18,19].

The management of CAT is particularly challenging due to the competing risks of thrombosis and bleeding. Low-molecular-weight heparin (LMWH) has long been considered the standard of care for treatment of CAT, based on studies demonstrating its superiority over vitamin K antagonists in reducing recurrence [20]. More recently, direct oral anticoagulants (DOACs), including apixaban, rivaroxaban, and edoxaban, have emerged as effective alternatives [21–23].

While DOACs are non-inferior to LMWH in preventing recurrent VTE, they may be associated with increased bleeding risk in patients with gastrointestinal or genitourinary cancers [22,23].

Current guidelines from major organizations, including the European Society of Cardiology (ESC), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN), recommend individualized anticoagulation strategies based on patient characteristics, cancer type, and bleeding risk [24–26]. Thromboprophylaxis is recommended for selected high-risk patients, particularly those receiving systemic therapy, while routine prophylaxis is not universally advised [25].

Despite advances in understanding and treatment, several challenges remain. These include optimal risk stratification, duration of anticoagulation, management in special populations (e.g., thrombocytopenia, renal impairment), and integration of biomarkers into clinical practice [27]. Furthermore, there is a lack of region-specific data, particularly in patients with hematologic malignancies, emphasizing the need for local clinical studies.

Aim

The aim of this study is to evaluate the clinical characteristics and prognosis of patients with cancer-associated thrombosis.

Primary objectives:

1. To determine the prevalence of risk factors and the most common comorbidities and their association with the occurrence and type of VTE in patients with a malignant process
2. To determine the prevalence of VTE type in active carcinoma:
   -pulmonary embolism,
   - deep vein thrombosis,
   -pulmonary embolism and deep vein thrombosis

Secondary objectives:

1. To evaluate the therapeutic efficacy of anticoagulant treatment (direct oral anticoagulants, low-molecular weight heparin, vitamin K antagonists), through:
   - Complete re-sewerage
   - Partial recanalization
   - Chronic occlusion

2. To determine the benefit of administered anticoagulant therapy (DOAC**,** LMWH, VCA), in relation to the occurrence of complications:
   - recurrence of thrombosis after 6 months,
   - major bleeding complications
   - clinically relevant non-major bleeding

Material and methods

Study Design and Population

This prospective, observational, single-center clinical study enrolled 30 patients with active cancer who were hospitalized at the University Clinic of Cardiology between October 2020 and October 2022.

Patients were categorized into three groups according to the location of venous thromboembolism (VTE):

1. Deep vein thrombosis (DVT)
2. Pulmonary embolism (PE)
3. Combined DVT and PE

Clinical characteristics and outcomes were compared among these groups.

Inclusion Criteria

- Patients were eligible for inclusion if they met the following criteria:
- Active cancer, defined as:
- Diagnosis within the previous 6 months, or
- Ongoing treatment within the last 6 months (chemotherapy, radiotherapy, hormone therapy, or surgery), or
- Presence of metastatic disease or cancer recurrence
- Objective diagnosis of:
- Deep vein thrombosis (DVT), and/or
    - Pulmonary embolism (PE)
    - Age $\geq$ 18 years
- Provided written informed consent

Exclusion Criteria

The following patients were excluded:

- Age < 18 years
- History of DVT prior to the diagnosis of active cancer

Data Collection and Clinical Assessment

All patients underwent comprehensive evaluation, including:

Clinical Assessment

- Medical history (anamnesis)
- Demographic data (age, sex)
- Risk factors and comorbidities:
    - Smoking
    - Obesity
    - Diabetes mellitus (DM)
    - Arterial hypertension (HTN)
    - Chronic kidney disease (CKD)
    - Hepatic disorders

Physical Examination

- Body mass index (BMI)
- Cardiopulmonary examination
- Lower extremity examination

Diagnostic Procedures

The following diagnostic methods were performed:

- Electrocardiography (ECG)
- Transthoracic echocardiography
- Color Doppler ultrasonography of lower extremity veins
- Computed tomography pulmonary angiography (CTPA), when pulmonary embolism was suspected

Laboratory Analysis

Routine laboratory tests included:

- Complete blood count
- Blood glucose
- Urea and creatinine
- Electrolytes (including potassium)
- Liver enzymes (AST, ALT, LDH)
- Hemostasis parameters:
- Activated partial thromboplastin time (aPTT)
- Thrombin time (TT)
- D-dimer levels

Treatment

Patients received anticoagulant therapy according to clinical indications, including:

- Direct oral anticoagulants (DOACs)
- Low-molecular-weight heparin (LMWH)
- Vitamin K antagonists (VKA)

Follow-up and Outcomes

Patients were followed at:

- 1 month
- 3–6 months

The following outcomes were assessed:

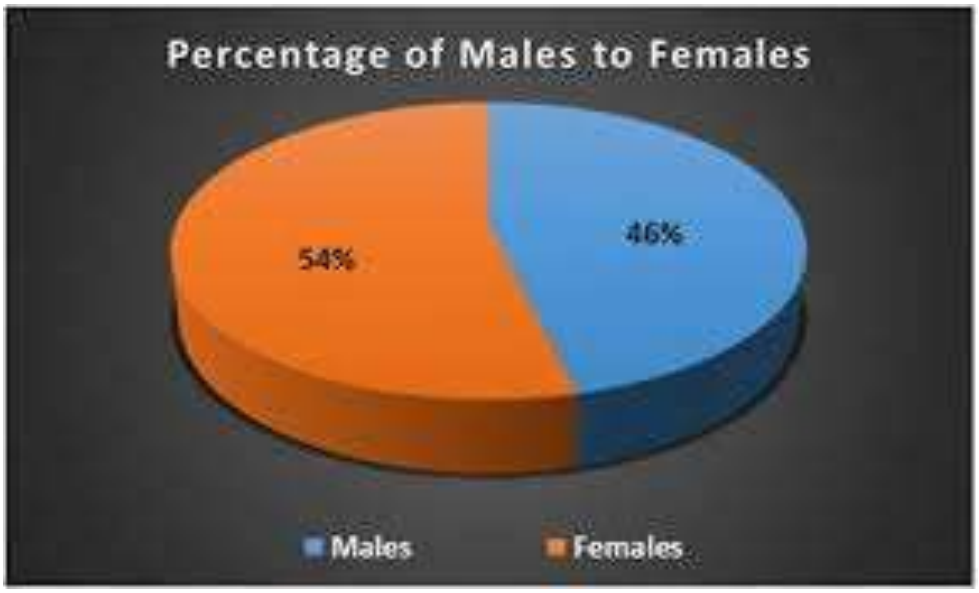
- Recurrence of VTE
- Major bleeding
- Clinically relevant non-major bleeding
- Overall survival

Follow-up evaluation included:

- Clinical assessment (history and physical examination)
- Doppler ultrasonography of lower extremity veins
- Echocardiography, when indicated

Results

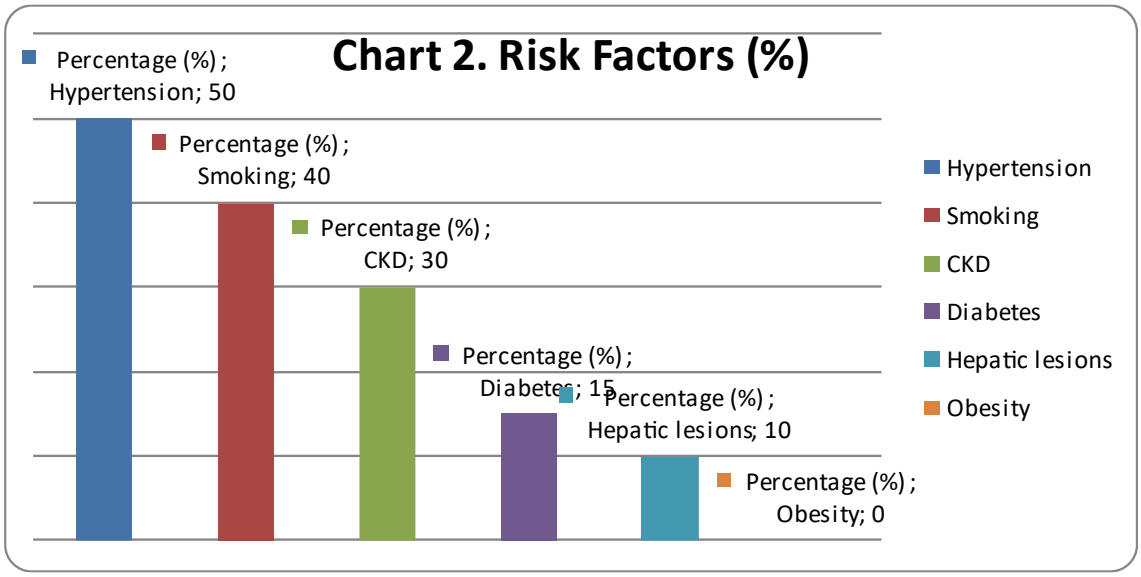
This prospective clinical pilot study included patients with previously diagnosed active carcinoma of various locations, in whom deep vein thrombosis (DVT), pulmonary embolism (BE), or a combination of DVT with BE occurred as a complication. The study included 20 patients, of whom 9 (45%) were women and 11 (55%) were men, with a mean age of 54 ±13.7 years (range 26 to 80) (Graphic No.1).



Graphic No.1. Distribution of males and females.

From clinical features, the prevalence of risk factors and comorbidities present was determined, with a higher prevalence in the male population. Most of the patients had hypertension (10 patients or 50%). The prevalence of chronic kidney disease was second (6 patients or 30%).

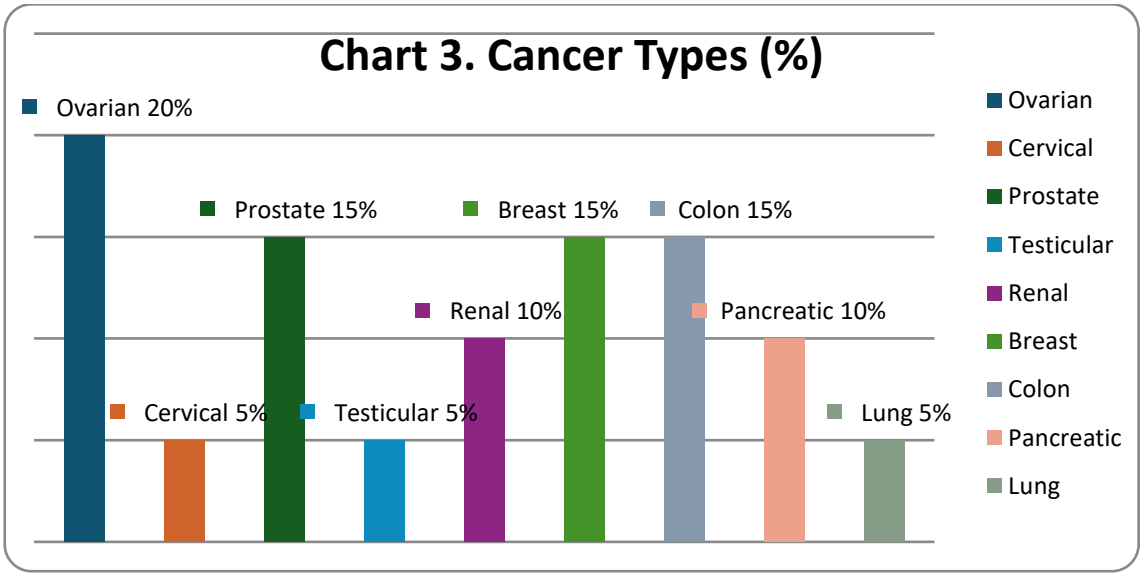
Three patients, or 15 percent, had diabetes. We identified a hepatic lesion in 2 patients or 10%. Smoking as a significant risk factor was observed in 8 patients, or 40%. Obesity as a risk factor was not represented in our group of patients (Graphic No. 2).



Graphic No 2. Risk factors present in cancer patients.

In terms of cancer type, our patients were dominated by urogenital carcinomas, specifically 4 patients with ovarian cancer and 1 patient with cervical uterine carcinoma (25%). In men, prostate cancer was present in 3 patients (15%), while testicular cancer was identified in 1 patient (5%).

Kidney cancer had 2 patients (10%). Breast cancer in our group accounted for 15% (3 patients). Of the carcinomas of the digestive system, the prevalence in our group was as follows: 3 patients or 15% were with colon cancer and 2 patients or 10% with pancreatic cancer. We identified lung cancer in 1 patient (5%) (Graphic No. 3).



Graphic No 3. Distribution of cancer types.

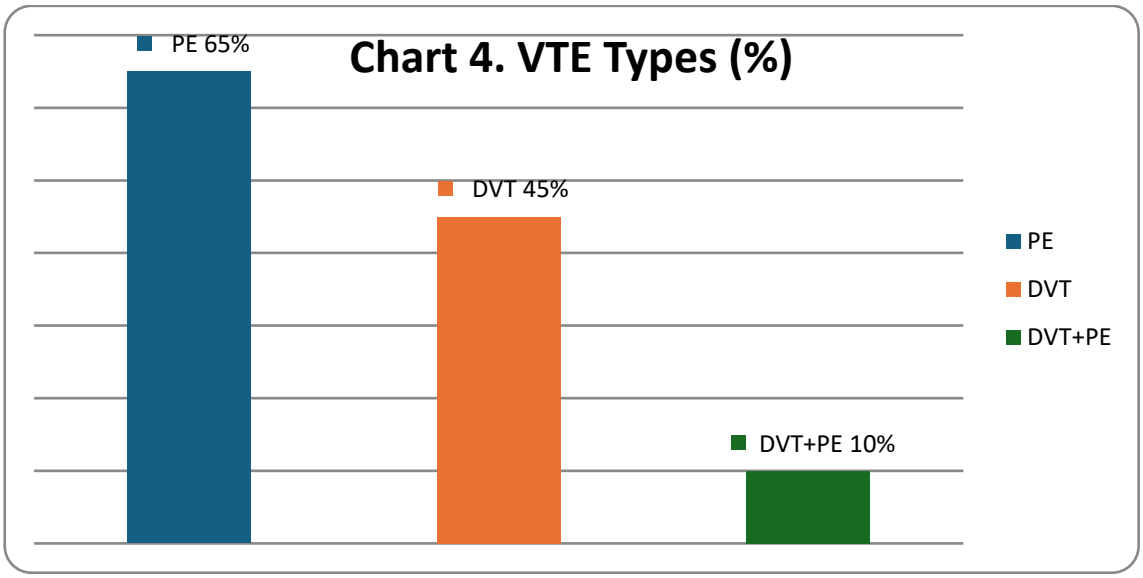
In terms of diagnostic procedures undertaken in our patients, in 9 patients (45%) we identified electrocardiographic features in addition to right-cardiac load (right-leaning axis, right branch block, pattern S1Q3T3). Echocardiographic findings in addition to right cardiac load with indirect signs of pulmonary thromboembolism were present in 50% (10 patients).

Color Doppler sonography of deep veins of the lower extremities diagnosed DVT in 45% (9 patients), in whom we had previously identified clinical symptoms and signs of deep vein thrombosis

(symptomatic DVT, 9 patients, or 45%). Computed tomography pulmonary angiography (CTPA) according to the pulmonary embolism protocol, according to a previously established indication, i.e. suspected PTE, was performed in 7 patients (35%), confirming the diagnosis of PTE, in patients who were transportable or hemodynamically stable.

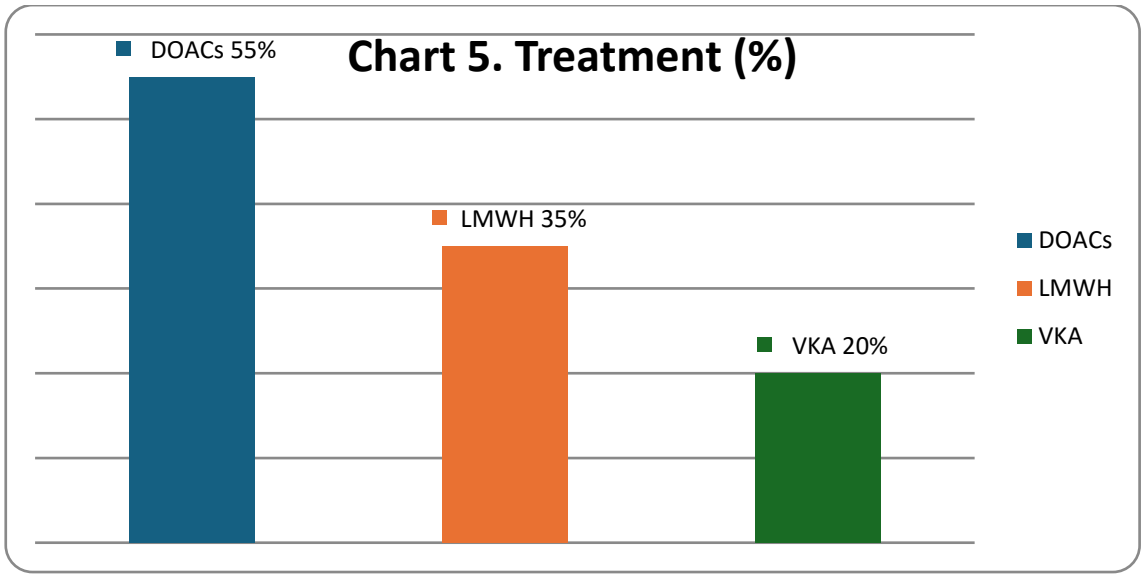
In terms of laboratory studies, the D dimer value was high in all patients, with a mean of 6854.31± 7567, and platelet values were within the reference range (150–350), except in 1 patient the Tr was low (below 100).

Using clinical and paraclinical trials, PTE was diagnosed in 13 patients (65%), DVT alone was detected in 9 patients (45%), and combined DVT with PTE was reported in 2 patients (10%) (Graphic No. 4).



Graphic No 4. VTE subgroups.

All patients were admitted immediately upon admission and suspected venous thromboembolism (VTE) was initiated with anticoagulant therapy while diagnostic procedures were ongoing. The most commonly used therapy in our group was direct oral anticoagulants (DOACs), which were administered as home therapy in 55% (11 patients). 7 patients (35%) were administered low molecular weight heparin (LMWH), and only 4 patients (20%) were prescribed with Vit.K antagonists (Graphic No.5).



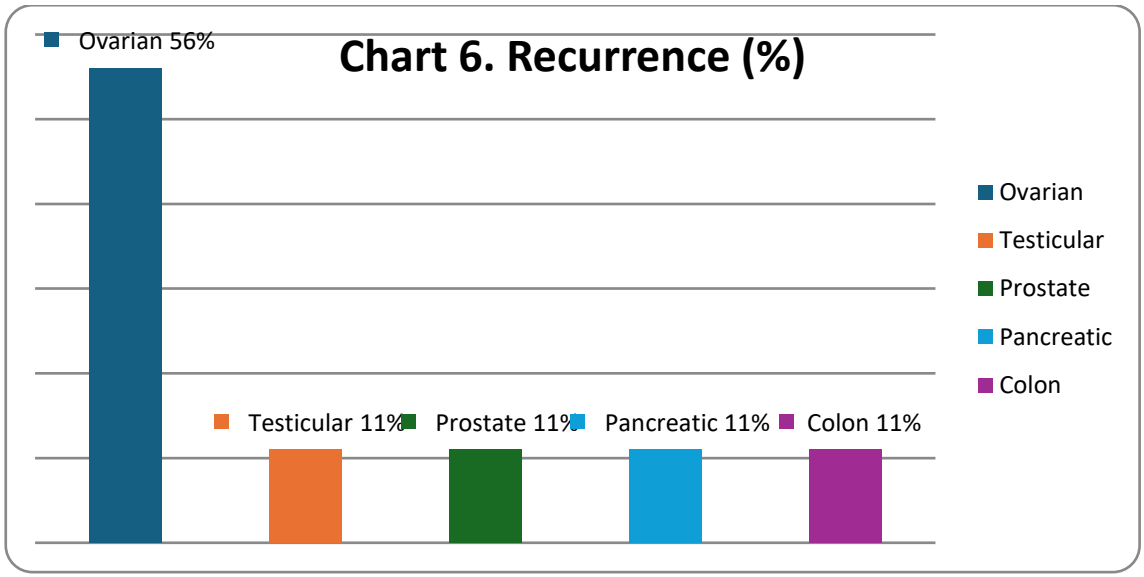
Graphic No 5. Anticoagulation therapy.

All patients were followed on an outpatient basis after 1 month of inpatient treatment and at 3–6 months, when the following clinical features were evaluated: onset of recurrence of thrombosis, occurrence of bleeding, and major bleeding, and clinically relevant non-major bleeding and death from all causes. Patients were monitored clinically (history and status) and laboratory (complete laboratory, with special consideration of D dimers and CCS).

According to the indications, the following diagnostic procedures were performed in patients: control color Doppler ultrasound of lower extremities veins, echocardiography.

In 9 patients we confirmed recurrence (45%) and in 3 patients (15%) major bleeding, which is why the DOAC was changed to LMWH. Clinically relevant non-major bleeding had 3 patients (15%) in whom DOAC was prolonged by dose reduction. No all-cause death was identified in our patient group after 6 months of follow-up.

In terms of the type of cancer, patients with genitourinary carcinomas had the most recurrence of thrombosis: ovarian cancer (5 patients, 56%), 1 patient with testicular cancer (11%) and 1 patient with prostate cancer (11%), (Chart No.6). In digestive carcinomas, recurrence was observed in 1 patient with pancreatic cancer (11%) and 1 patient with colon cancer (11%) (Graphic No.6).



Graphic No 6. Recurrence of thrombosis in different cancer types.

Discussion

In this prospective unicentric pilot study, we analyzed 20 hospitalized patients with cancer-associated venous thromboembolism (VTE) involving malignancies of different anatomical locations. The gender distribution was nearly balanced, with 45% female and 55% male patients.

The mean age was 54 years, with a relatively wide range (26–80 years), indicating the presence of VTE even in a younger patient population (<50 years), which is clinically relevant.

Our findings demonstrated that the most common malignancies associated with VTE were **genitourinary cancers**. Among female patients, 25% had ovarian (n=4) or cervical cancer (n=1), while breast cancer was present in 3 patients (15%). In the male population, genitourinary malignancies were also prominent, with prostate cancer (n=3) and testicular cancer (n=1), together accounting for 20% of the cohort. Additionally, renal cancer was identified in 2 patients (10%). These findings are consistent with existing literature identifying high-risk tumor types for thrombosis [28,29].

The second most frequent group of malignancies associated with VTE in our cohort were **gastrointestinal cancers**, with colon cancer present in 3 patients (15%) and pancreatic cancer in 2 patients (10%). Pancreatic cancer, in particular, is well recognized as one of the malignancies with the highest thrombotic risk [30,31]. Lung cancer was less represented in our study (5%), likely due to the limited sample size.

The management of cancer-associated thrombosis (CAT) has evolved significantly in recent years. Current international guidelines recommend **direct oral anticoagulants (DOACs)** as an effective alternative to **low-molecular-weight heparin (LMWH)** for both initial and long-term treatment of CAT in selected patients [32–34].

Several randomized controlled trials (RCTs) have evaluated the efficacy and safety of DOACs compared with LMWH. A pooled analysis of six RCTs including 3,690 patients demonstrated that DOACs significantly reduced the risk of recurrent VTE compared to LMWH (RR 0.67; 95% CI 0.52–0.85) [35,36].

Regarding safety, major bleeding events were numerically higher in the DOAC group but did not reach statistical significance (RR 1.17; 95% CI 0.82–1.67) [35]. However, clinically relevant non-major bleeding was significantly more frequent in patients receiving DOACs (RR 1.66; 95% CI 1.31–2.09) [36].

Importantly, no significant difference in all-cause mortality was observed between DOAC and LMWH treatment groups, supporting comparable overall survival outcomes [35–37].

These findings support the use of DOACs as an effective and convenient therapeutic option for cancer-associated thrombosis, particularly due to their oral administration and improved patient adherence. However, careful patient selection remains essential, especially in individuals with gastrointestinal and genitourinary malignancies, where bleeding risk may be increased [38,39].

In our cohort, venous thromboembolism (VTE) recurrence was observed in 9 patients (45%) during follow-up, indicating a relatively high recurrence rate compared with larger randomized trials. This finding is likely influenced by the small sample size, heterogeneity of malignancies, and the advanced stage of cancer in many patients, all of which are well-established risk factors for recurrent thrombosis.

Direct oral anticoagulants (DOACs) were the most frequently used treatment modality in our study and were associated with both recurrence and bleeding events. Major bleeding occurred in 3 patients (15%), leading to a switch from DOAC therapy to low-molecular-weight heparin (LMWH). In addition, clinically relevant non-major bleeding (CRNMB) was observed in 3 patients (15%), necessitating dose reduction of DOAC therapy. These findings are consistent with evidence from randomized controlled trials, which demonstrate a higher incidence of clinically relevant non-major bleeding with DOACs, particularly in patients with gastrointestinal and genitourinary malignancies.

LMWH was primarily used in patients at higher risk of bleeding or following complications during DOAC therapy. In our cohort, LMWH demonstrated a favorable safety profile, particularly in patients who developed bleeding complications, supporting its role as a preferred option in high-risk clinical scenarios. This observation aligns with current guideline recommendations, which favor LMWH in patients with increased bleeding risk, including those with gastrointestinal cancers or thrombocytopenia.

Vitamin K antagonists (VKA) were less frequently used and played a limited role in our study population. Given their variable pharmacokinetics, need for regular monitoring, and potential drug–drug interactions, VKAs are generally considered less favorable compared to DOACs and LMWH in cancer-associated thrombosis.

Overall, our findings highlight the importance of individualized anticoagulant therapy in patients with cancer-associated thrombosis. While DOACs offer convenience and efficacy in reducing recurrence, they may be associated with an increased risk of bleeding in certain patient populations. Conversely, LMWH remains a safer alternative in patients with high bleeding risk or in those who develop complications during DOAC therapy. The balance between thrombosis recurrence and bleeding risk remains a critical consideration in optimizing treatment strategies for this complex patient population.

Conclusion

There is growing evidence supporting the use of direct oral anticoagulants (DOACs) as an effective and safe treatment option for venous thromboembolism (VTE) in selected patients with cancer. DOACs offer several advantages, including oral administration, predictable pharmacokinetics, and improved patient adherence, making them an attractive alternative to traditional therapies.

However, low-molecular-weight heparins (LMWHs) remain an important treatment option in patients at increased risk of bleeding. This includes patients with gastrointestinal malignancies, chemotherapy-induced thrombocytopenia, those receiving anticancer therapies with potential drug–drug interactions involving shared hepatic metabolic pathways, and patients with intracranial tumors or brain metastases.

Therefore, the choice of anticoagulant therapy in cancer-associated thrombosis should be individualized, taking into account tumor type, bleeding risk, comorbidities, potential drug interactions, and patient preferences. A tailored, patient-centered approach remains essential to optimize clinical outcomes.

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