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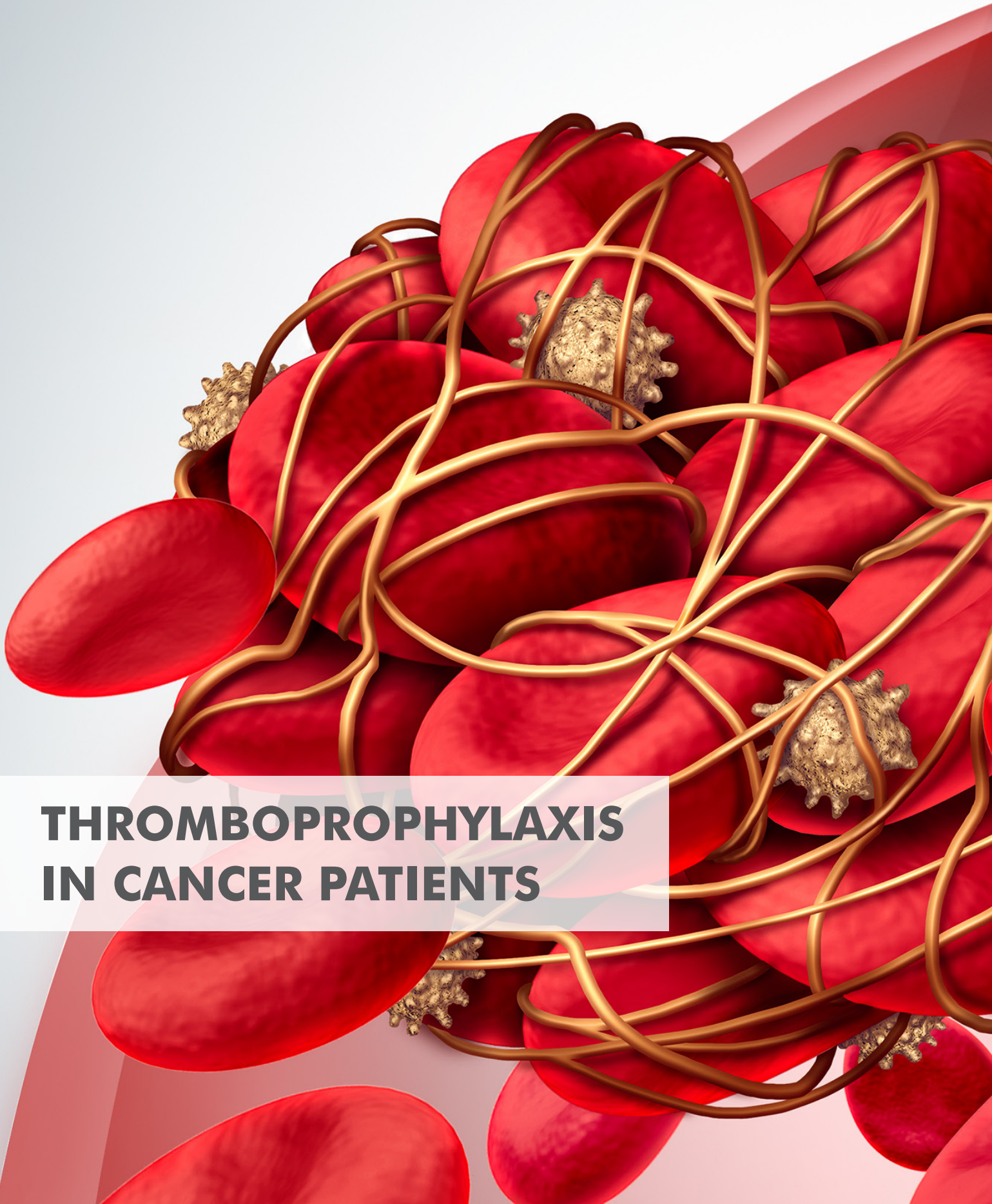

THROMBOPROPHYLAXIS IN CANCER PATIENTS

Learning Objectives

At the end of this educational content, the reader will gain a fair idea about:

1. Burden associated with venous thromboembolism (VTE) in patients with cancer
2. Various risk factors associated with VTE in patients with cancer
3. VTE risk assessment models to identify and stratify patients with cancer who need thromboprophylaxis

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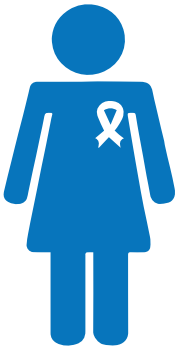
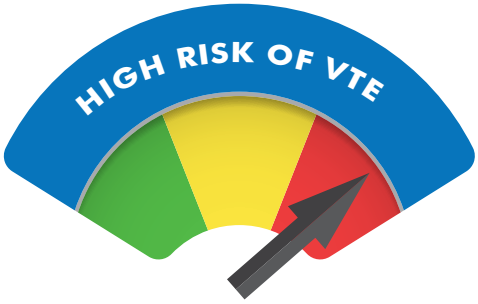
Epidemiology



Cancer is a hypercoagulable state where the patients are at **high risk of developing VTE**.[1]

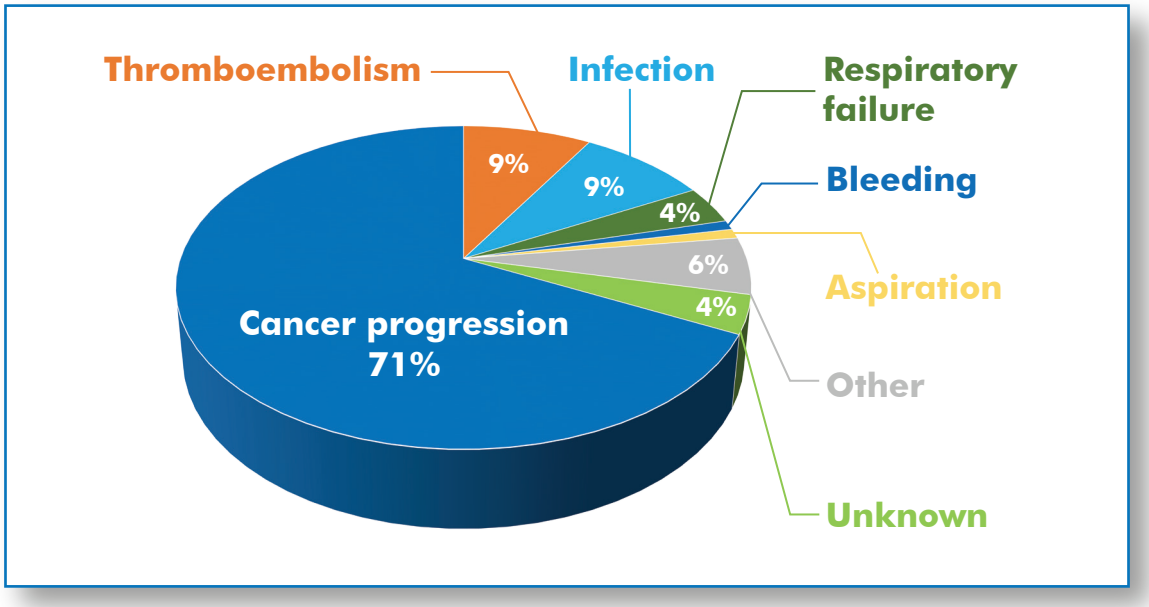
In India, the most common **predisposing factor for VTE** is a **malignancy (31%)**.[2]



Cancer patients have a higher risk of **first (six-fold)** and **recurrent VTE (three-fold)** compared to non-cancer patients.[3]

VTE is the second leading cause of death in patients with cancer (Figure 1).[3]

Figure 1: VTE: The second leading cause of mortality in patients with cancer



Causes of death exceed total number of deaths because six patients had more than one cause of death identified

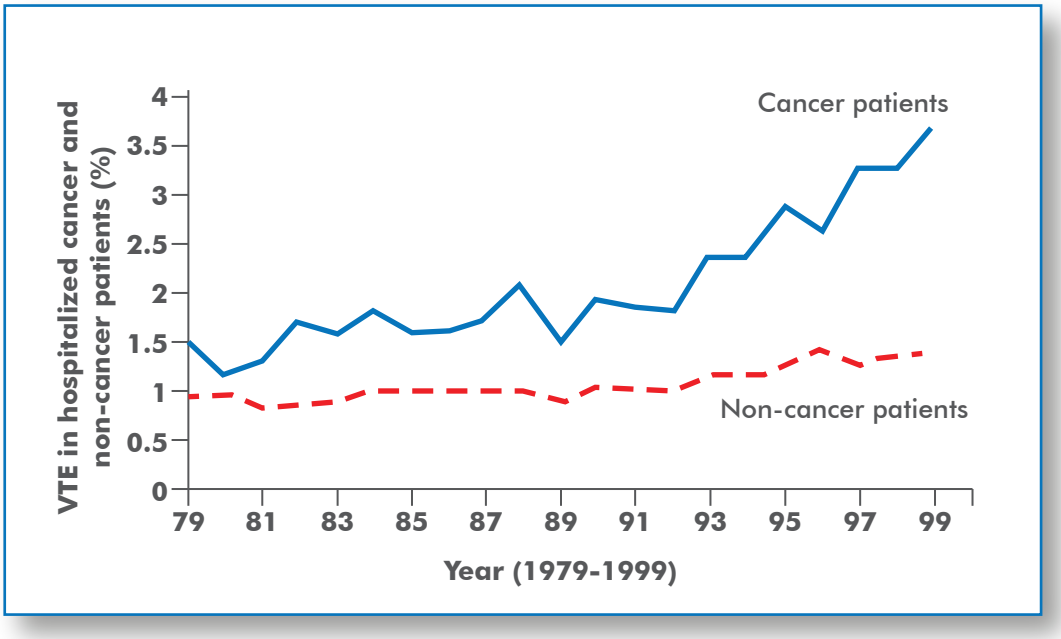
- VTE accounts for **9% of deaths in patients with cancer**.[4]
- A **47-fold increase in the risk of death** from VTE is reported in cancer patients **receiving systemic chemotherapy** compared to the general population.[4]
- VTE is associated with **early mortality** during **chemotherapy**.[5]

20% of all cancer patients will have symptomatic VTE.[6]

There is an increased risk of major bleeding (2.2 times) as compared to non-cancer patients.[7]

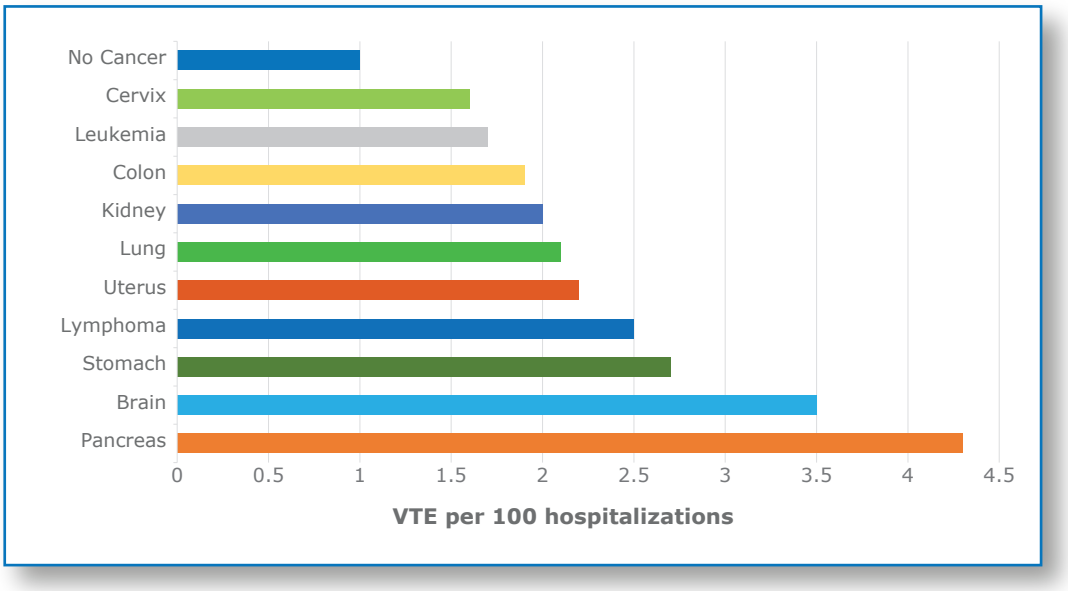
- The **risk of VTE is increased by seven times in hospitalized cancer patients** compared to hospitalized non-cancer patients.[7]
- In a study conducted between 1979–1999, it was found that the incidence of VTE in hospitalized cancer patients increased sharply as compared to hospitalized non-cancer patients (Figure 2).[7]

Figure 2: Incidence of VTE in patients hospitalized with cancer vs. non-cancer patients



The incidence of VTE among patients hospitalized with cancer (Figure 3)[8]:

Figure 3: Incidence of VTE among patients hospitalized with cancer



Higher risk cancers: Pancreatic, brain, gastric, hematologic malignancies (Lymphoma, Myelomas), uterus, lung and renal.

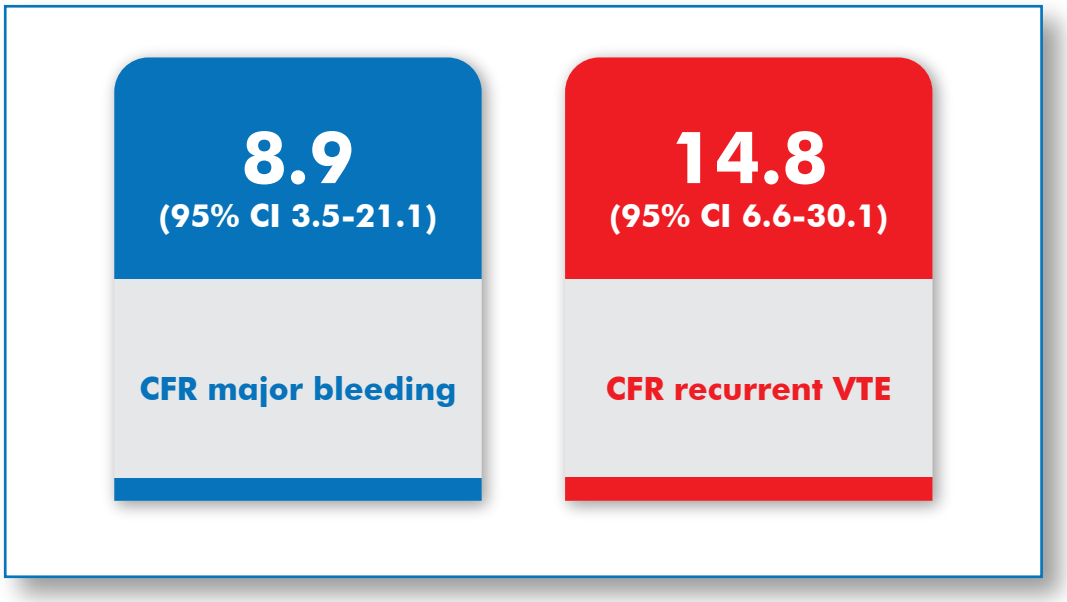
An analysis including 29 studies was conducted from 1980 to 2019. Results showed that[9]:

Rates of recurrent VTE and fatal recurrent VTE were 23.7 and 1.9 per 100 patient-years follow-up, respectively. The incidence of case fatality rate was 14.8%.

Rates of major bleeding and fatal major bleeding events were 13.1 and 0.8 per 100 patient-years of follow-up, respectively. The incidence of case fatality rate was 8.9%.

The case fatality rate of recurrent VTE was higher than the case fatality rate of **major bleeding in patients with cancer.**

Figure 4: Case fatality rates (CFR) of recurrent VTE and major bleeding in patients with cancer

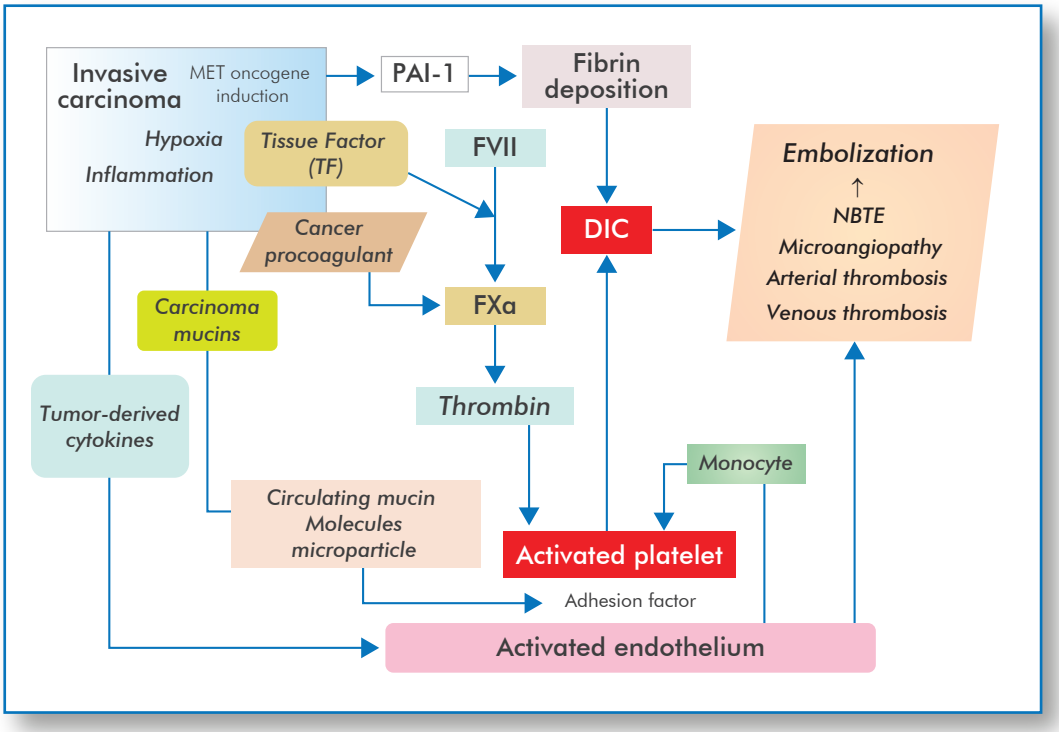


Mortality rates for recurrent VTE are higher than those for bleeding events.[10]

Pathophysiology in CAT

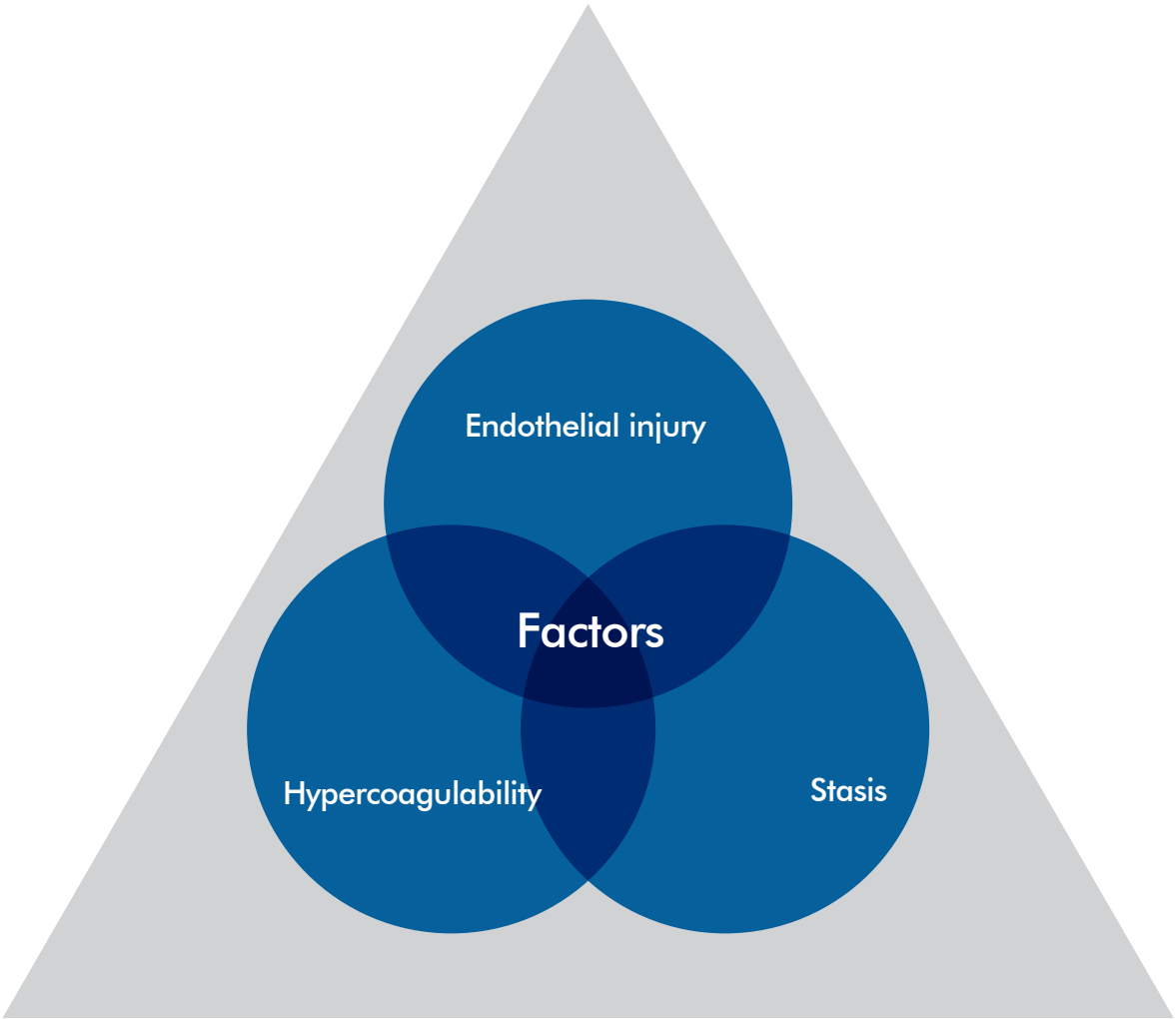
Increased incidence of thrombosis in patients with cancer can be attributed to its multiple, overlapping, and interacting pathophysiology (Figure 5).[11]

Figure 5: Pathophysiology of cancer-associated thrombosis



- Malignant cells produce tissue factor that triggers the coagulation cascade leading to the formation of Factor Xa.[12]
- Some cancer cells can produce cancer procoagulant that acts directly on Factor Xa.[12]
- Chemotherapy has also shown to be a cause of cancer-associated thrombosis.[12]
- Chemotherapeutic agents, including methotrexate, cyclophosphamide, cisplatin, doxorubicin, 5-fluorouracil, and lenalidomide, have been found to increase the risk of VTE and mortality.[12]

Various factors can lead to the formation of thrombus in cancer patients (Virchow's triad). These include[13]:



These three broad categories of factors together comprise the **Virchow's Triad**.[3]

Endothelial injury: Damage to endothelial vessels can result from

- Smoking
- Chronically elevated blood pressure
- Atherosclerotic disease secondary to hyperlipidemia

Hypercoagulability: Can occur due to

- Pregnancy
- Use of oral contraceptive medications
- Cancer
- Chemotherapy drugs
- Thrombophilia (Protein C deficiency, Protein S deficiency, antithrombin deficiency, hyperhomocysteinemia, homocystinuria, antiphospholipid syndrome)

Stasis: Most likely to occur in patients with

- Atrial fibrillation
- Valvular heart disease
- Prolonged immobility (bedridden patients)
- Surgery
- Trauma

Risk factors for CAT

Risk factors for CAT include[14,15]

Patient-related factors

- Advanced age
- Female gender
- Prior history of thromboembolism
- Medical comorbidities (Charlson Comorbidity Index [CCI] ≥3)
- Presence of varicose veins
- Infection, obesity, anemia, pulmonary or renal disease
- Prolonged immobilization
- Hereditary factors (Factor V Leiden)

Tumor-related factors

- Site of cancer:
  - Very high risk: Stomach, pancreas, brain
  - High risk: Lung, kidney, hematological, gynecological
- Stage: Advanced stage and an initial period of diagnosis
- Histological grade of the tumor
- Time since cancer diagnosis

Treatment-related factors

- Hospitalization
- Surgery
- Platinum-based chemotherapy and other types of chemotherapy
- Hormonal therapy
- Anti-angiogenic therapy
- Radiotherapy
- Erythropoiesis-stimulating agents
- Blood transfusions
- Central venous catheter

Biomarkers

- Platelet count
- Leukocyte count
- D-dimer
- Tissue factor expression by tumour cells
- Circulating tissue factor
- Soluble P-selectin
- C-reactive protein
- Prothrombin fragment 1+2

Risk Assessment Models (RAMs) for VTE

The Khorana score

The American Society of Clinical Oncology (ASCO) guidelines 2019 recommend **Khorana score** for ambulatory patients with solid tumors on treatment with systemic therapy.[16]

The Khorana score is a simple and user-friendly tool that **helps identify and stratify the risk of VTE in patients with cancer** (Table 1).[17,18]

Table 1: The Khorana score for cancer-associated thrombosis

Patient characteristic	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynaecologic, bladder, testicular)	1
Prechemotherapy platelet count ≥350 x 10^9/L	1
Hemoglobin level <100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count >11 x 10^9/L	1
BMI 35 kg/m^2 or more	1

0 points = Low risk
1-2 points = Intermediate risk
≥3 points = High risk

Case Study - 01

A 76-year-old woman presented to the hospital with a 4-week history of intermittent chest pain radiating to the back. The routine examination revealed that her hemoglobin level was low (<10 g/dL). An upper endoscopy was performed, which showed a large ulcerated tumor in the body of the stomach. Histological examination revealed moderately differentiated adenocarcinoma.

What is the VTE risk in this patient according to the Khorana score?

A. Low risk

B. Moderate risk

C. High risk

D. None of the above

Answer: **C**

Explanation: The patient has a total score of 3, denoting a high risk of VTE.

Patient characteristic	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynaecologic, bladder, testicular)	1
Prechemotherapy platelet count ≥350 x 10^9/L	1
Hemoglobin level <100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count >11 x 10^9/L	1
BMI 35 kg/m^2 or more	1

The PROTECHT score

In the **PROTECHT score**, the Khorana score is modified by adding chemotherapy agents, such as platinum-based regimens and gemcitabine, which **improves the predictive performance of identifying patients at high risk of VTE** (Table 2).[17,19]

Table 2: The PROTECHT score for cancer-associated thrombosis

Patient characteristic	Risk score
Pancreatic or gastric cancer (very high-risk tumors)	2
Lung, gynecological, lymphoma, bladder, or testicular (high-risk tumors)	1
Pre-chemotherapy hemoglobin <10 g/dl or use of erythropoietin-stimulating agents	1
Pre-chemotherapy white blood cell count >11 x 10^9 /L	1
Pre-chemotherapy platelet count ≥350 x 10^9/L	1
Body mass index >35 kg/m^2	1
Gemcitabine chemotherapy	1
Platinum-based chemotherapy	1
0–2 points = Low risk patients **≥3 points = High-risk patients**	

Case Study - 02

A 60-year-old obese man (BMI >35 kg/m^2) was admitted to the hospital for neutropenic fever and placed on intravenous antimicrobials. He had a medical history of pancreatic adenocarcinoma stage IIB and was undergoing treatment with gemcitabine-based chemoradiation and post-radiation gemcitabine.

What is the estimated VTE risk in this patient according to the PROTECHT score?

A. High risk

B. Moderate risk

C. Low risk

D. None of the above

Answer: **A**

Explanation: The patient has a total score of 4, indicating a high risk of VTE

Patient characteristic	Risk score
Pancreatic or gastric cancer (very high-risk tumors)	2
Lung, gynecological, lymphoma, bladder, or testicular (high-risk tumors)	1
Pre-chemotherapy hemoglobin <10 g/dl or use of erythropoietin-stimulating agentsa	1
Pre-chemotherapy white blood cell count >11 x 10^9 /L	1
Pre-chemotherapy platelet count ≥350 x 10^9/L	1
Body mass index >35 kg/m^2	1
Gemcitabine chemotherapy	1
Platinum-based chemotherapy	1

0–2 points = Low risk patients
≥3 points = High-risk patients

Other risk prediction models for VTE in cancer[20]

VTE risk CONKO score

Incorporated risk factors

- Tumor site of origin:
  Very high risk: stomach, pancreas
  High risk: lung, lymphoma, gynecologic, bladder, testicular
- Prechemotherapy platelet count ≥350 × 10^9/L
- Hemoglobin level <10 g/dL or use of erythropoiesis-stimulating agents
- Prechemotherapy leukocyte count >11 × 10^9/L
- WHO performance status ≥2

VTE risk COMPASS-CAT score

Incorporated risk factors

- Breast, lung, ovarian, or colorectal cancer only
- Cancer-related risk factors:
  - Anthracycline or anti-hormonal therapy in women with breast cancer
  - Time since cancer diagnosis ≤6 months
  - Central venous catheter
  - Advanced cancer stage
- Predisposing risk factors: Cardiovascular risk factors (≥2 of peripheral artery disease, ischemic stroke, coronary artery disease, hypertension, hyperlipidemia, diabetes, obesity)
- Recent hospitalization for acute medical illness
- Personal history of VTE
- Prechemotherapy platelet count ≥350 × 10^9/L

Take Home Points

- VTE is the 2nd leading cause of death in cancer patients, which accounts for 9% of deaths in cancer patients.[4]
- Risk factors for CAT may be patient-related, tumor-related, or treatment-related. Certain biomarkers may help further stratify the VTE risk.[15]
- The Khorana score and the PROTECHT score are the most employed scores in identifying and stratifying VTE risk.[17]

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