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# CANCER-ASSOCIATED THROMBOSIS: AN OVERVIEW OF THROMBOSIS MECHANISMS AND ITS RISK FACTORS IN CANCER

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**ABSTRACT:** Thrombosis is one of the major causes of death and disability worldwide. Cancer patients are commonly thrombophilia or prothrombotic since they have abnormalities in all three factors of Virchow's triad, which lead to thromboembolism. Venous thrombosis (VT) is a chronic disorder that has the potential to be fatal and cause considerable complications. Venous thromboembolism (VTE) may potentially be the first indication of an undetected cancer in individuals. The rate of VTE and the risk of complications are much higher in the cancer patient groups. Arterial thrombosis is more likely to form when the plaque on the wall of the arteries consists a significant quantity of lipids covered by a layer of connective tissue. Thrombus formation in arteries may result in a heart attack or stroke. The hemostasis phase (liquid blood quickly hardens and forms a clot following injury to the blood vessel wall) spirals out of control. As a result, many blood clots form in the blood vessels that provide blood to various organs. Patients display paradoxically both excessive and inadequate clotting. The coagulation cascade begins when one of these proteins is proteolytically cleaved. Clotting factors then activate the subsequent clotting factor, and so forth. The production of many blood clots depletes the body's platelets and clotting components. Cancer patients have a 5-fold greater incidence of VTE. Thrombosis is the second most common, but often preventable, cause of mortality among cancer patients. Age-related variables such as reduced activity due to increased age, less energy to perform activities, increased inactivity, and overall coagulation activation raise one's risk. The risk of thromboembolism varies according to the histologic subtype of cancer. Anticancer drugs can cause a prothrombotic condition by a variety of mechanisms. VTE is three times more common in individuals with non-small cell lung cancer with adenocarcinoma. Individuals with cancer are more likely to experience increased frequency of hemostatic conditions. Cancer promotes the activation of blood coagulation, resulting in thrombophilia. Various biomarkers may be useful in determining people with cancer at high risk of acquiring venous thromboembolism. P-Selectin has also been shown to play a part in the interactions between tumours and their host cells as well as immunity from malignant cells.

**INTRODUCTION:** Thrombosis is one of the large causes of loss and ill health worldwide [1, 2].

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Thrombosis is mainly divided into two sub-categories or forms in either arteries or veins.

DVT occurs in the lower part of the body, where a blood clot is formed and attached to the walls of the veins, known as a thrombus, or may get detached and travel through the blood to different sites of the body, known as embolism [3, 4].

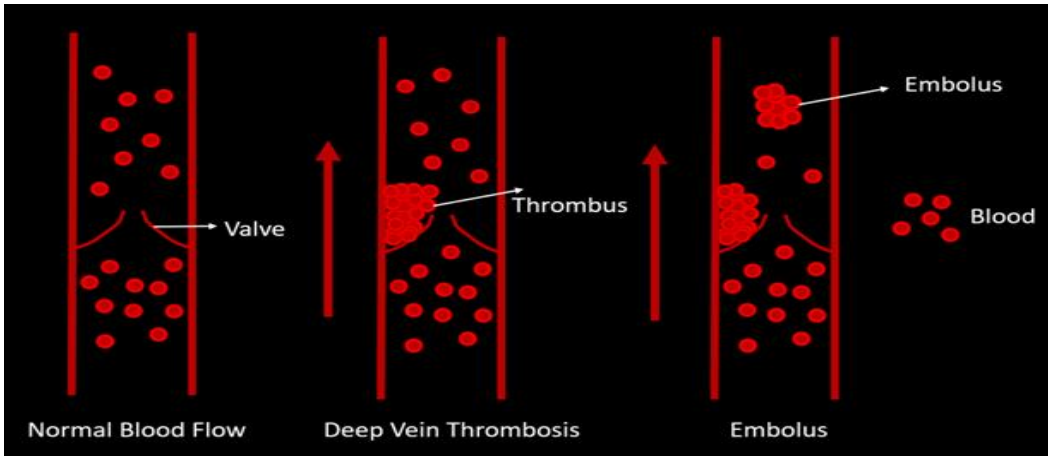


**FIG. 1: REPRESENTATION OF THROMBOSIS IN VASCULATURE**

Thromboembolism in Cancer patients may extend from artery or vein thrombosis to widespread intravascular coagulation [5, 6]. Despite the known link between tumor & venous thromboembolism disorder, the mechanisms promoting thrombotic conditions in patients with cancer are not well understood & seem to be complex [7]. Patients with cancer are commonly thrombophilia or prothrombotic, since they have abnormalities in all 3 factors of Virchow's triad, which lead to thrombosis. After Carotid artery stenosis, Brain hemorrhage, dementia, and Peripheral vascular disease, Pulmonary Embolism and venous thrombosis are among the most prevalent vascular illnesses [8]. As far as we know, Pulmonary embolism is a side effect of deep vein thrombosis or we can say it is typically a consequence of DVT (deep vein thrombosis). Multiple risk factors are causing Venous thromboembolism (VTE), including Genetic predisposing conditions which can be genetic or developed at some earlier stage of life, abnormal clotting, reduced tendency to lysis a clot, lack of protein C, protein S or other naturally present anti-coagulants in a body, smoking, obesity, long term period exposure to high altitude [9-12]. Additional Risk Factors to form a thrombus include post operation patients, post child birth period in females, and a person diagnosed with cancer [13, 14].

**Virchow's Triad:** Venous thrombosis is mainly developed by three major components characterized by Rudolf Virchow and named as Virchow's triad, consisting of three elements: hypercoagulability, abnormal blood flow, and endothelial injury. Hypercoagulability comes from genetic deficits or autoimmune conditions. WBC plays an important part in the progress of deep vein thrombosis. Any inflammatory condition, such as trauma (acute, chronic, or complex), an operation, or an illness, may damage the inner lining of the blood vessel, which can further cause DVT. Blood stagnation beyond the site of damage, or venous stasis, causes disturbances in blood flow, which can further result in stroke and pulmonary embolism.

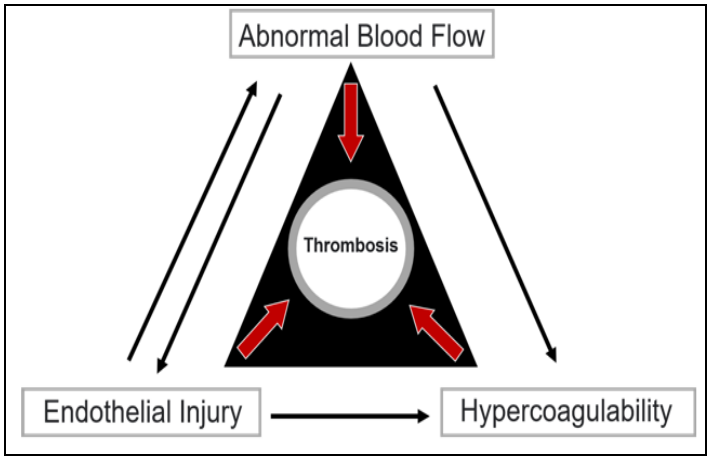


**FIG. 2: REPRESENTATION OF VIRCHOW'S TRIAD**

**Relation between Cancer and Thrombosis:**

**Venous Thromboembolism (VTE):** Thrombosis is a chronic disorder that has the potential to be fatal and cause considerable complications. Numerous pathophysiological processes connect thrombosis and cancer; the rate of DVT and the risk of problems are much higher in patients with cancer groups compared to different patient groups [15]. Thrombosis may potentially be the first indication of undetected cancer in individuals. Among malignant patients, thrombosis is the 2nd largest important cause of death. Tumor type, surgery, and chemotherapy are the major causes of cancer-related venous thromboembolism (VTE); indications of venous thromboembolism for specific people are just beginning to emerge [16]. Cancer patients with symptomatic venous thromboembolism after therapy were likelier to perish early than those without VTE. Anticoagulation may directly change tumour biology to increase long-term survival in this group, which raises the issue given that VTE seems to impact cancer-related deaths and disabilities. The advantages of successful VTE methods in cancer patients are well-documented in published guidelines [17]. By conducting an ideal risk assessment and following local & global procedures for the avoidance& management of VTE, the healthcare professional may improve patient outcomes in partnership with the patient and their caregivers [18].

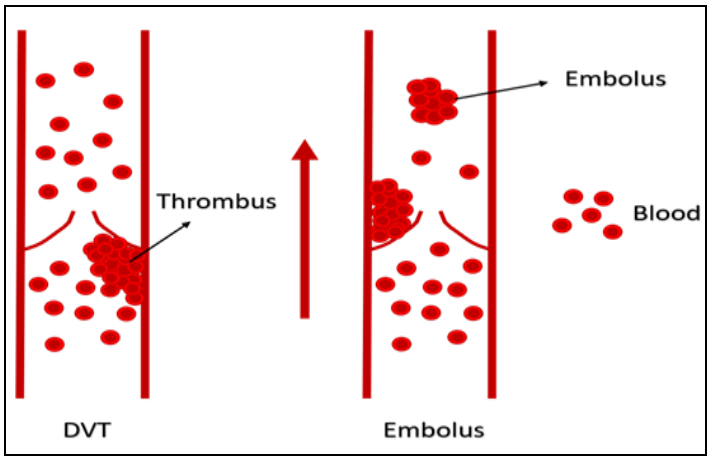


**FIG. 3: REPRESENTATION OF DEEP VEIN THROMBOSIS (DVT) AND EMBOLUS**

**Arterial Thrombosis:** Despite the fact that there isn't as much data about thrombosis in arteries in malignant patients compared to thrombosis in veins (Venous thromboembolism). Acute arterial thrombosis has been linked to new cancer in many case studies [19]. Recent research by Navi *et al.* examined the connection concerning cancer patients & the frequency of thrombosis in arteries in a massive matched-group study. At 180 days, the rate of coronary thrombosis was 4.8% in malignant patients versus 2.3% in matched controls [20].

Arterial thrombosis is more likely to form when the plaque on the wall of the arteries consist of a significant quantity of lipid covered be a layer of connective tissue. When an endothelial wall is damaged, either by an undisturbed plaque or by a damaged plaque, the chances of arterial thrombosis may increase [21]. Due to the rupture, procoagulant molecules that are preset inside the plaque result in platelet activation, which further induces arterial thrombosis [22]. Renal artery stenosis Due to plaque, the arteries become narrowed, preventing adequate blood flow within the arteries, which helps form a clot that consists of platelets as their main component, as platelets can stick even at a high velocity. Thrombus formation in arteries may result in a heart attack or stroke.

However, it should be well-known that arterial thrombosis in patients with tumours can form even in the lack of a plaque, for instance, in patients with heart conditions [23]. In this case, systemic thrombophilia is triggered due to a number of components secreted by malignant cells, such as thrombin & VEGF, which promote platelet activation and coagulation [24, 25].

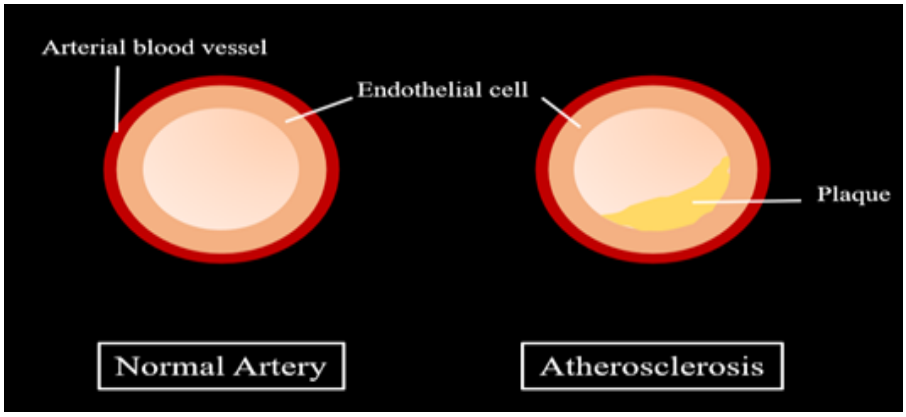


**FIG. 4: REPRESENTATION OF NORMAL ARTERY AND ATHEROSCLEROSIS**

**Chronic Defibrination Syndrome:** The term "defibrination syndrome" refers to a condition in which the hemostasis phase (liquid blood quickly hardens and forms a clot following injury to the blood vessel wall) spirals out of control. As a result, many blood clots form in the blood vessels that provide blood to various organs, resulting in organ dysfunction [26]. Disseminated intravascular coagulopathy, or consumptive coagulopathy, is an alternative term for defibrination syndrome, because continuous clotting exhausts the body's platelets and clotting factors. Even a tiny incision in the artery walls might lead to bleeding in other body regions if there are insufficient platelets in the blood. Patients display paradoxically both excessive and inadequate clotting. Normally, if the endothelial wall is damaged or if there is a cut, there is immediate constriction of blood vessels (by small muscles in their walls), narrowing the blood vessel and lowering the blood flow. Some platelets then stick to the ruptured vascular endothelial wall and start to change their shape and activate, activating other platelets to combine and form a plug-like structure. The process of forming a platelet plug on the ruptured wall from inactivated platelet cell is known as platelet plug formation (primary hemostasis). Consequently, the secondary hemostasis (coagulation cascade) is initiated [27].

The initial group of clotting factors in the blood consists mostly of proteins produced by the liver; however, these proteins are not active and float in the body. The clotting cascade begins after 1 of the proteins is proteolytically cleaved. The next clotting factor is subsequently proteolytically activated by this active protein, and so on. This cascade proceeds swiftly and with a high degree of amplification, from damage to clot formation. Fibrinogen must be triggered to produce fibrin, which sums and polymerizes to create web around the platelet, adhering to the platelet and expanding into a web. Consequently, the actions that occur before the fibrin strengthens the platelet plug are part of the secondary hemostasis process, which clues to the creation of a dense clot at the place of the wound. As soon as a clot develops, the body begins to eliminate it. This prevents the clot from becoming larger than necessary and ensures that it dissolves when it is no longer required (fibrinolysis) [28]. Normally, fibrinolysis and clot formation are in a constant state of equilibrium. In sepsis, cancer, major trauma or intravascular hemolysis (blood type incompatibility), the release of a procoagulant can shift the equilibrium in favour of clot development. Procoagulants may be bacterial chemicals or TF (tissue factor) such as LPS (lipopolysaccharide). Clotting factors may also be proteolytically cleaved and activated by enzymes. The coagulation cascade then goes into overdrive, resulting in considerable clot formation that obstructs small and medium blood vessels, eventually leading to organ loss or ischemia. The kidneys, brain, and liver are among the most vulnerable organs. The production of many blood clots depletes the body's platelets and clotting components. When fibrinolysis degrades clots, the breakdown products enter the circulation, preventing platelets from adhering together and forming clots, making it more difficult to halt bleeding [29].

**Factors affecting Cancer-Associated Thrombosis:** Malignant patients are diagnosed with all forms of thrombosis, such as systemic disorders, including disseminated intravascular coagulation (DIC), venous and arterial thrombosis,

and more. The most thoroughly researched thrombotic issue in cancer patients, who make up a vulnerable group, is venous thromboembolism (VTE). These sufferers had a 5-fold greater incidence of VTE than the overall population [30]. In a historical group study, thromboembolism was determined to be the 2nd common, but often avoidable, reason for mortality among cancer patients, behind the disease itself. In a group-based control-case analysis of VTE health conditions, Malignant patients had a three- to five-fold higher incidence of thromboembolism matched to individuals without malignancies [31].

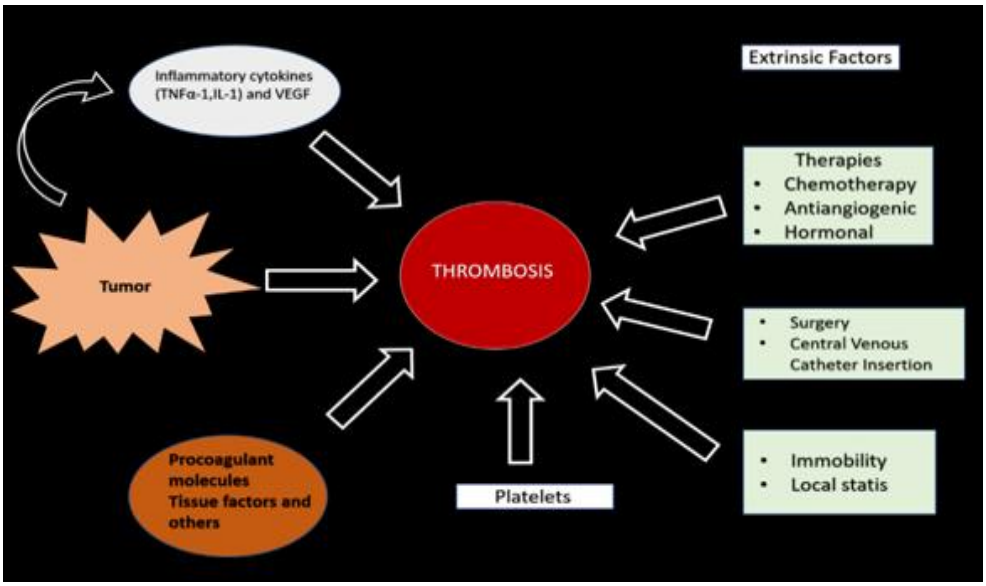


**FIG. 5: CANCER-ASSOCIATED THROMBOSIS RISK FACTORS**

**Individual Risk Factors Related to Patients:** Age-related variables, such as reduced activity due to increased age and less energy to perform activities, increased inactivity, and overall coagulation activation, raise one's risk of thromboembolism, regardless of malignancy. Large prospective research indicated that patients with cancer aged Eighty-five and up were nearly ten times more likely to be diagnosed with thromboembolism at an incidence rate of 6.96 per 1000 people than people aged forty-five to fifty-five (0.72 per 1000 people) [32]. This proves that people of increased age have a higher chance of being diagnosed with thrombosis than patients who are young in a cancer population.

Cancer patients are expected to be diagnosed with VTE if they are on touch rest for 3 or more days and are less active. The chances of venous thromboembolism are increased due to abnormal blood flow caused by less activity or immobility [33]. Patients with DVT who are diagnosed earlier are also more likely to be diagnosed with thrombosis after cancer, as they have a 5-fold higher incidence of DVT than patients who are not diagnosed with DVT [34, 35].

**Cancer-Associated Risk Factors:** Several cancer-linked risk variables, containing cancer origin, phase, histological subtype, & timeframe ever since identification, may influence the risks of cancer-related thrombosis (CAT). It is crucial to highlight that comparing venous thromboembolism rates across various patients in the published research is sometimes challenging due to changes in research methodology, patient groups, data collection procedures, and follow-up intervals [36].

**Diagnosed Period:** Malignant patients have an elevated possibility of coagulation caused by cancer (cancer-associated thrombosis) during the early diagnosis phase, and the risk reduces over time [37, 38]. As most of the therapeutic treatments like chemotherapeutic treatments take place during this period [39].

The research was done for venous thromboembolism (VTE) within 90 days after diagnosis, in which the odds ratio was 54, dropping to 14 and 4 in the interval periods of three months to one year and one-to-three-year periods, respectively [40].

**Stage of Cancer:** Patients who are at a later stage of cancer have an increased incidence of thrombosis caused by cancer (CAT). Among hematologic malignancies, lymphoma and multiple myeloma had the greatest risk for cancer-associated thrombosis (CAT), whereas brain and gastrointestinal tumors had the highest cancer-associated thrombosis (CAT) risk in solid malignancies [41]. The risk of thromboembolism varies according to the histologic subtype of cancer. VTE is three times more mutual in individuals with non-small cell lung cancer with adenocarcinoma than in those with squamous cell carcinoma [42].

**Medications in Cancer:** Patients using anticancer medications or undergoing anticancer treatments like chemotherapy are more likely to develop CAT [43, 44]. Anticancer drugs can cause a prothrombotic condition by a variety of mechanisms containing vascular endothelial injury, decreased intensities of endogenous anticoagulants, stimulation of tissue factor procoagulant activity, and platelet triggering [45, 46].

**Therapy using Chemicals (Chemotherapy):** Combining chemical (chemotherapeutic) medications raises the frequency of venous thromboembolism in people with breast cancer, however, the underlying mechanism remains uncertain [47, 48]. In addition, chemotherapy raises the danger of venous thromboembolism & induces a prothrombotic phase by a variety of diverse mechanisms [49, 50] that may directly injure the endothelial wall, reduce natural anticoagulant chemicals, and/or elevate the procoagulant protein (prothrombin, fibrinogen) [51]. Chemotherapy may also induce apoptosis and cytokine release, which can result in increased tissue factor (TF) production, which is regarded as the natural promoter of coagulation [52]. which further states that using chemotherapy as a therapy for cancer may result in platelet activation.

Cytotoxic and chemotherapy are both linked to venous thromboembolism. Cisplatin causes the death of endothelial cells and the release of procoagulant endothelium microparticles. VTE is a problem in individuals with acute lymphoblastic leukemia after asparaginase inhibitor treatment, & symptomatic VTEs may be minimized with low-molecular-weight heparin (LMWHs) [53-56].

5-Fluorouracil depletes protein C, boosts thrombin activity, and destroys endothelial cells, promoting thrombus formation [57]. Tamoxifen is one more example of an anti-estrogen medication. Its estrogenic action increases the possibility of venous thromboembolism by depleting protein C and protein S [58, 59].

Not only is chemotherapy linked to a higher risk of venous thromboembolism, but the type of cancer is also linked to the amplified danger of thrombosis [60]. VTE risk is already significant in those with advanced pancreatic cancer; if these patients are treated with chemotherapy, it may worsen it. Additionally, low molecular weight heparinas thromboprophylaxis for three months reduced that risk; nonetheless, continued anticoagulation growth may be useful to reduce a potential thromboembolic possibility in the future [61]. CAT has developed possibilities due to added new anticancer agents, immunotherapeutic medications, or chemotherapeutic drug combinations [62].

**Radiation Therapy:** When the possibility of VTE is high in the early stages of cancer, radiotherapy may be used as part of localized treatment, which can be combined with or without chemotherapy for some tumors [63]. Consequently, there is evidence that radiation may influence the efficacy of anticoagulant usage for venous thromboembolism in malignant patients [64]. Radiation exposure impacts the coagulation factors pathway (the protein C pathway) and its interaction with an endogenous anticoagulant protein (thrombomodulin) [65]. After exposure to radiation, procoagulant factors, including activated factor VIII, pro-inflammatory nuclear factor kappa B, enhanced D-dimers, and pro-thrombin fragments, stimulate the procoagulant reaction [66]. Radiation also causes primary hemostasis by activating TF and von Willebrand factors [66], which results in endothelial dysfunction and thrombosis. Furthermore, an *in-vitro* research found that tumour irradiation stimulates cancer cell integrin αvβ3, which plays a critical function in cancer-associated thrombosis [66].

**Hormonal Therapy:** Hormone treatment is an identified risk factor for cancer progress & it increases the possibility of VTE, potentially strengthening the link between cancer-related thrombosis and thrombosis-related cancer [67, 68].

**Surgical Procedures:** Surgical procedures are well-identified reasons for venous thromboembolism (VTE). Patients who acquire venous thromboembolism (VTE) after an operation have an increased death rate [69]. In addition, a time-consuming surgery has been associated with a greater possibility of thrombosis [70]. Several factors, including increased fibrinogen levels, thrombin production, TF activation, reduced fibrinolysis, and blood coagulation, may result in a prothrombotic condition [71]. In addition, patient immobility after surgery might result in deep venous thrombosis and the upregulation of cancer procoagulants, which cause rapid injury to the vascular endothelium [72]. Other variables that may enhance the likelihood of VTE development during surgery include pelvic dissection, the posture of the patient during surgery, malignancies, old age, and cardiac attack or lung failure [73].

**TABLE 1: FACTORS AFFECTING THROMBOSIS IN CANCER PATIENTS**

| Patient correlated | Cancer correlated | Treatment correlated |
|---|---|---|
| Longer periods of rest on bed | Site of cancer | Surgical procedures |
| History of thrombosis | Stage of cancer after diagnosis | Chemotherapy |
| Increasing age | | Antiangiogenic treatment |
| Excessive amount of body fat | | Transfusions of blood |

**Cancer-Associated Thrombosis:** Due to the various procedures adopted, different groups studied, and methods of diagnosing venous thromboembolism (VTE), it is challenging to evaluate research covering the incidence of venous thrombosis in malignant sufferers. Individuals with cancer are more likely to experience increased frequency of hemostatic conditions. Cancer promotes the initiation of blood clotting, resulting in thrombophilia. Even without thrombotic or excessive bleeding (hemorrhagic) symptoms, such patients' irregularities in one or more coagulation tests are typical. Laboratory markers of blood coagulation activation correlate with cancer progression and are increasingly severe in individuals with metastases. The TAT (thrombin-antithrombin) complex, coagulation factor IX and X activation peptides, prothrombin fragment F1 + 2 (F + 2), fibrinopeptides A and B, fibrin degradation products, D-dimer, and plasmin-antiplasmin complex are among the new laboratory tests that can detect subtle changes in the hemostatic system [74].

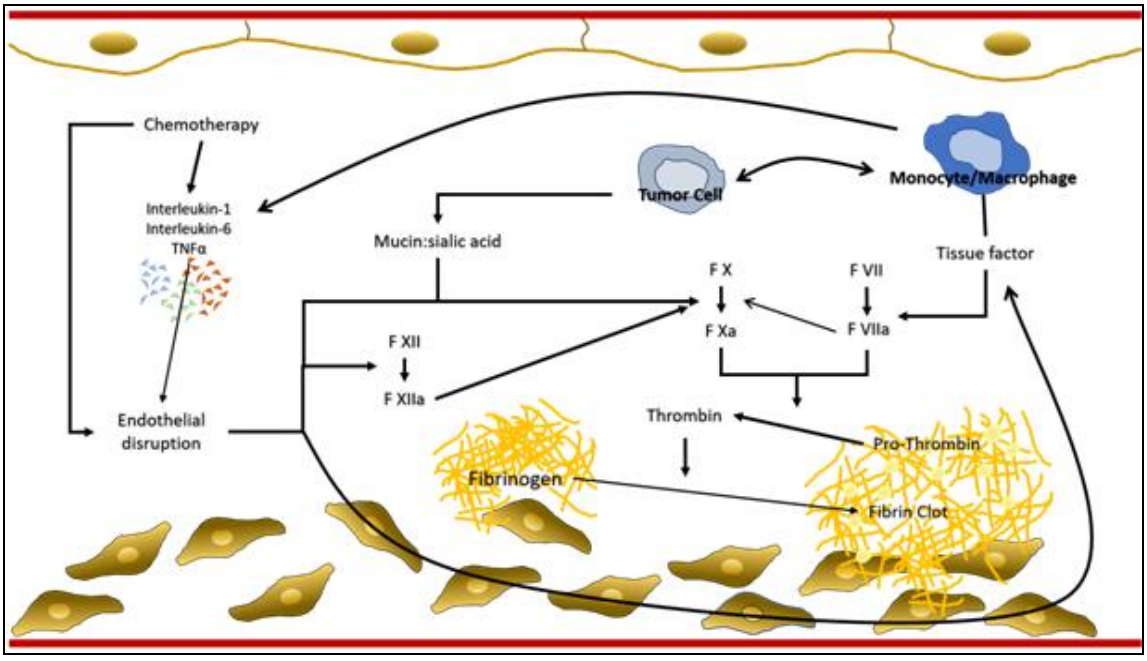


**FIG. 6: MECHANISM OF CANCER-ASSOCIATED THROMBOSIS**

Only a few observational studies have assessed the accuracy of blood coagulation marker values (platelet count, clotting time, partial thromboplastin time, prothrombin time, and Factor XIII test) in predicting the progress of venous thrombosis in malignant sufferers. Researchers showed that preoperative thrombin–antithrombin complex stages were good predictors of post-surgical deep vein thrombosis (DVT) in patients receiving surgery for abdominal malignancy [75, 76].

Various research has identified a number of diagnostic biomarkers that may be useful in determining people with cancer at great possibility of acquiring venous thromboembolism (VTE) and who may benefit from primary prevention and treatment for thrombosis. A pre-chemotherapy platelet count of more than 350,000 platelets per microliter predicted future thrombosis during chemotherapy in a prospective analysis of cancer patients receiving chemotherapy [77, 78]. Recent studies from the Vienna Cancer and DVT study reveal that increased P-selectin levels help in predicting thromboembolism [79, 80] and amplified D-dimer levels, in addition to Factor1 and Factor 2, are linked with an amplified risk of VTE in these individuals.

**Mechanisms Involved in CAT:**

**Platelets:** Platelets can be activated by tumor cells by direct and indirect pathways that ultimately result in thrombosis [81, 82]. Additionally, TCIPA (tumor-cell-induced platelet aggregation) was associated with increased metastatic potential [83]. A key tumor-cell-induced platelet aggregation mechanism is cancer cell procoagulants' release of thrombin, which converts fibrinogen to fibrin. Another method is activating platelet-expressed coagulation factors V, VIII, XI and XIII and PAR receptors (protease-activated receptors) [84].

Additionally, tumour cells secrete adenosine diphosphate (ADP), which stimulates platelets to release additional adenosine diphosphate, further activating additional platelets [85]. Additionally, platelets express TF on their membrane, contributing to cancer-associated thrombosis [86]. Platelets include several growth factors, which are also found in the tumour environment, which help in the development of cancer cells and support angiogenesis [87-89].

**Coagulation:** TF and cells and platelets are crucial for hemostasis. Clotting consists of three overlapping stages: beginning, magnification, and spreading [90]. During the initiation phase, TF binds to factor VIIa to trigger factor IX and factor X. The stimulation of factor IX connects the extrinsic and intrinsic pathways. Then, factor Xa binds to factor II to produce thrombin.

Because the quantity of thrombin produced is insufficient to create a broad clot, positive feedback loops are present to bind thrombin with platelets, initiating the amplification phase. Enzyme complexes (tenase complex and prothrombinase complex) on the platelet surface enable high levels of thrombin production and platelet activation during the propagation phase [91]. This ensures continuous thrombin production, followed by fibrin and polymerization to produce a strong clot [92, 93].

**P-Selectin and Cancer:** A broad array of cell adhesion molecules in our bodies interact with their surroundings. Intercellular and intracellular interactions are all mediated by cell adhesion molecules (CAMs). Aside from cell adhesion, CAMs affect cell growth and motility, inflammation, and numerous signal transduction pathways [94]. P-Selectin is a protein that belongs to the selectin family. P-Selectin is produced by a range of cell types, including platelets, endothelium, & immunological cells, as well as malignant cells. Because of its high expression by activated platelets, P-selectin (SELP) is significant in the pathophysiology of general thromboembolism and cancer-linked thrombosis. The process through which P-Selective causes thromboembolism is linked to events that might help form tumours, such as inflammation. SELP has also been shown to play a part in the interactions between tumours and their host cells and immunity from malignant cells [95]. As a result, SELP has been the subject of several research examining its function in the development of cancer [96].

**Connection between Cancer-associated Thrombosis and Thrombosis-associated Cancer:** Cat and Tac have a strong bond. Cancer patients may experience a prothrombotic condition, and tumor spread due to the coagulation system activated by tumor cells secreting procoagulant,

fibrinolytic, pro-inflammatory, and pro-angiogenic cytokines [97]. In comparison, coagulation factors influence the growth of malignancies that lead to TAC. Previous research revealed that hemostatic problems in malignant patients might contribute to the recruitment of inflammatory cells, the development of the tumour stroma, and angiogenesis [98]. TF is known to be expressed on endothelial cells, platelets, cancer cells, and TF-bearing EVs, contributing to the thrombotic phenotype seen in cancer patients [99, 100]. The TF/factor VIIa complex influences blood coagulation, inflammation, and angiogenesis [101]. Cancer patients or metastases may have elevated TFPI-1 levels owing to TF absorption in tumour cells or injured endothelium cells in continuing coagulation activity [102]. TF also controls v3 integrin, which is expressed on platelets, cancer cells, and endothelium, as described before. Activation of Integrin v3 promotes tumour angiogenesis and progression [103]. In conclusion, TF isoforms, factor VII, PAR2, and v3 integrin influence cell process and cell contact with their surroundings, including angiogenic processes [104].

**CONCLUSION:** There have been major improvements in our knowledge of the association between cancer & thrombosis and the major risk issues for VTE in malignant patients in recent years. Cancer-associated thrombosis shows unique features that distinguish them from ordinary VTE cases. Among all cancer types, few cancers are particularly prone to VTE, along with chemotherapy and advanced-stage cancer. Management of CAT requires a very specific approach to other causes of VTE. LMWH is still the first treatment choice and has proved to be as efficient and safe. Cancer patients admitted for major surgery need primary prophylaxis against VTE as a treatment approach.

However, the mechanism & factors affecting DVT in cancer patients remain less understood and require more specific approaches. A deeper understanding of cancer-associated thrombosis is needed to prevent and diagnose DVT due to cancer, is further need to be worked out.

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**CONFLICTS OF INTEREST:** Nil

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