Chapter

# Thrombotic Events in Cancer Patients

*Azin Alizadehasl and Haniye Hajiali Fini*

## Abstract

Cancer poses the highest clinical and social burden throughout the world and is the second cause of death after is chemic heart disease, although will be predicted the first in 2060. Cancer patients are high risk for thrombotic events that are characterized as the second cause of death after cancer itself. Thrombotic events seem to be increasing over recent years according to improved patients survival, novel thrombogenic cancer treatment and central catheter using. As we know thromboprophylaxis reduces the risk of VTE and primary prevention seems to be more effective way to reduce morbidity and mortality in these patients several criteria was designed to reduce this risk. Khorana risk score is the most important of them which designed for ambulatory cancer patients. Some other risk factors for thrombotic events consist of major abdominal surgery and prolonged immobility after surgery, use of thrombogenic medications (chemotherapy agents), old age, obesity, distant metastasis or advanced stage at the time of diagnosis, hyperthermic intraperitoneal chemotherapy (HIPEC) as a new surgery technique, anemia that requires blood transfusion that recommend special attention should be paid to them.

**Keywords:** cancer, cancer-associated thrombosis, thromboprophylaxis, Khorana score, venous thromboembolism, arterial thromboembolism, cardiotoxicity, cardiooncology

## 1. Introduction

Cancer poses the highest clinical and social burden throughout the world which is nonsignificantly higher in men than women. The risk of developing cancer is 20.2% for lifelong (22.4% in men and 18.2% in women). Cancer is the second cause of death after ischemic heart disease, although it will be predicted the first in 2060 [1]. The Studies demonstrated 19.3 million new cancer patients and about 10 million cancer deaths occurred in 2020 [2].

Breast cancer has recognized as the most common malignancy followed by lung, liver, colorectal, prostate, and stomach cancers [1, 2]. Despite breast cancer prevalence outstrip lung cancer over the time, the most common causes of death include lung, liver, and stomach cancers, respectively [2, 3].

Thrombus can involve either veins or arteries and is associated with substantial morbidity and mortality as the third most common cardiovascular disease [4]. Acute vein and artery thrombosis is computed as the most common causes of death in developed country. The epidemiology of thrombus depends on if it is venous versus

arterial, provoked versus unprovoked, or first episode versus subsequent episode. Thrombus etiology is multifactorial [5]. Main components of thrombus consist of fibrin, platelets, red blood cells (RBCs), leukocytes [6]. Thrombosis occurs with low shear flow and intact endothelial wall in veins and is associated with severe shear, damaged endothelial wall, and platelet-rich clot formation in arteries [4]. Vein thrombosis is more common due to low velocity of venous blood flow. Sedentary lifestyle, immobilization, contraception agents, pregnancy, surgery, coagulation disorders, high haematocrit level and increased blood viscosity, varicose veins, obesity, infectious disease, and using intravenous drug can contribute to it [4].

Vein or artery thrombus can break away and be transferred to lung or cerebral and peripheral vessels, respectively. Thus, it is important to protect thrombus formation or be diagnosed and start adequate treatment as soon as possible [4].

Cancer patients are high risk for both venous and arterial thromboembolism that are characterized as the second cause of death after cancer itself. Malignancies are responsible for about 18% of all cases with venous thromboembolism (VTE) [7, 8]. Venous thrombosis prevalence in patients with cancer is four- to sevenfold higher compared to healthy individuals [8], and some research reported this risk may be increased up to 28-fold in certain malignancies [7]. A study showed that arterial thrombosis assigns about 5.6% of death in cancer patients. Thrombotic events seem to be increasing over recent years according to improved patients survival, novel thrombogenic cancer treatment, and using central catheter. Venous thromboembolism (VTE) in cancer patients is not limited to deep veins and pulmonary embolism, unusual sites of thrombosis are reported such as upper extremities and cerebral or splanchnic veins. Arterial thromboembolism (ATE) also manifests as myocardial infarction (MI) or cerebrovascular accident (CVA) predominantly [8].

## 2. Risk factors of thrombosis in cancer patients

### 2.1 Patient-related risk factors include as follows

- Age of 70 years or older—aging is accompanied by increased immobility and systemic activation of coagulation.
- Black ethnic—some studies suggested higher rate of thrombosis in black patients with cancer, although data show conflicting too.
- Immobility—bed rest of greater than 3 days is related to higher rate of thrombotic events.
- Poor functional status.
- Inherited coagulation disorders such as antithrombin (AT), protein C and protein S deficiency, or factor V leiden and factor II G20210A are related to thrombotic events at younger age.
- Medical comorbidities such as heart disease, obesity, infection, respiratory disease, renal disease, and anemia lead to 1.5-fold and higher risk for thrombus formation in cancer patients.

- Prior history of thromboembolism—risk of venous thromoembolism (VTE) recurrence is about six- to sevenfold in patients with malignancy and history of VTE [8, 9].

### 2.2 Cancer-related risk factors are delineated based on malignancy site, stage, histopathology, and time after diagnosis

- Malignancy site—the highest risk for thrombotic events is for pancreatic cancer and then primary brain tumor, stomach, esophagus, uterus and ovarian, lung cancers, and hematologic malignancies such as non-hodgkin lymphoma and multiple myeloma.

- Malignancy stage—researches show that almost half of cancer patients with thromboembolism at time of cancer diagnose have advanced stage or metastasis. A study reported fourfold increased risk of venous thromboembolism (VTE) in cancer patients without metastasis compared to increased 58-fold in patients who had distant metastasis.

Peritoneal surface malignancy (PSM) can be a manifestation of cancer metastasis from colorectal or ovarian malignant sites. Although, new methods of treatment such as cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPECH) can improve survival, these procedures are related to activating of coagulation cascade. Postoperative venous thromboembolism risk in PSM patients is as high as 30-50% without thrombo prophylaxis.

- Tumor histopathology—the studies have shown that histological subtypes of some cancers may have different risk for thrombotic events.

- Time after cancer diagnosis: 3–6 months after cancer diagnosis is highest risk full time for thrombotic events. Although, some other research suggest that greatest risk of thromboembolism is within the first year following diagnosis [8–10]. Eventually, this risk decreases within 10 years after cancer diagnosis [11].

### 2.3 Treatment-related factors—thrombotic events can increase with surgery, anticancer therapies, and supportive care in cancer patients

- Chemotherapy agents—using some chemotherapeutic agents lead to increase two- to sixfold risk of thrombosis. Cisplatin regimen has a known effect in this way and increases risk for both vein and arterial thrombosis events. Immunomodulatory agents like thalidomide and lenalidomide can increase risk for venous and arterial thromboembolism, about 1.98% for myocardial infarction (MI) and 3.4% for cerebrovascular accident (CVA). Bevacizumab, a monoclonal antibody against vascular endothelial growth factor receptor (VEGFR), increases the risk of arterial rather than the vein thromboembolism events.

- Hospital admission for acute medical illness or surgery (especially pelvic and abdominal cancer surgery) is associated with increasing risk of thrombosis formation. The reports demonstrated two- to threefold risk of thrombotic events in these cases.

- Supportive care—supportive treatment including erythropoiesis-stimulating agents, red blood cell, and platelet transfusion lead to venous thromboembolism in cancer patients [8, 9].

Central venous catheters are important access to delivery of intravenous drugs in cancer patients. The incidence of catheter-related thrombosis is estimated about 5–30% and can interrupt chemotherapy treatment or cause substantial morbidity including pulmonary emboli and post-phlebitic syndrome [9].

Recent studies reported that high leukocyte and platelet counts and low hemoglobin level are associated with higher risk of venous thromboembolism in patients with malignancy [8].

## 3. Cancer-associated thrombosis mechanisms

Patients with malignancy often have several predisposing factors for thrombus formation. Traditionally, Virchow's triad including stasis, thrombophilia, and endothelial damage have a critical role in pathophysiology of thromboembolism in these patients. Tumor compression and bed rest condition can lead to blood stasis. Homeostasis disturbance, hypercoagulable state, and inflammation have a key role in pathogenesis of thrombosis. Endothelial dysfunction can be the result of abnormal tumor vascularity as a mechanism for thrombosis formation [4, 12–14]. Cancer can conduce to the presence of antiphospholipid antibody, decrease in hepatic anticoagulant synthesis, and reduced hepatic clearance of coagulation factors, too [14]. Finally, imbalance between procoagulative factors and fibrinolytic system lead to cancer-associated thrombosis [12].

### 3.1 Directed mechanism of cancer-associated thrombosis: several factors expressed on or released from cancer cells

- Tissue factor (TF) is the most important tumor-derived procoagulant protein that expresses on tumoral cells as an initiator of extrinsic pathway in coagulation cascade and results in the activation of factor II and fibrin synthesis and platelet activation. Although, the relation between tumor TF expression and risk of thrombotic events has been observed only in pancreatic and ovarian cancers.

- Microparticle (MP) is membrane vesicle that is released from cancer cells, and its procoagulative effect is associated with the expression of active tissue factor on it which cause platelet activation and thrombus formation. Although, this relation between microparticles and thrombotic events has only been in pancreatic cancer.

- Podoplanin (PDPN) is expressed by cancer-associated fibroblasts and causes platelets activation and aggregation. It has been reported in pancreatic cancer cells.

- Plasminogen activator inhibitor- (PAI-1) has been shown to be expressed on pancreatic cancer cells and is an inhibitor of fibrinolysis, thus increasing the risk of thrombosis formation.

- Cancer cells can secrete and generate platelets agonists such as adenosine diphosphate (ADP) and thrombin that cause platelets activation and aggregation [9, 12, 15].

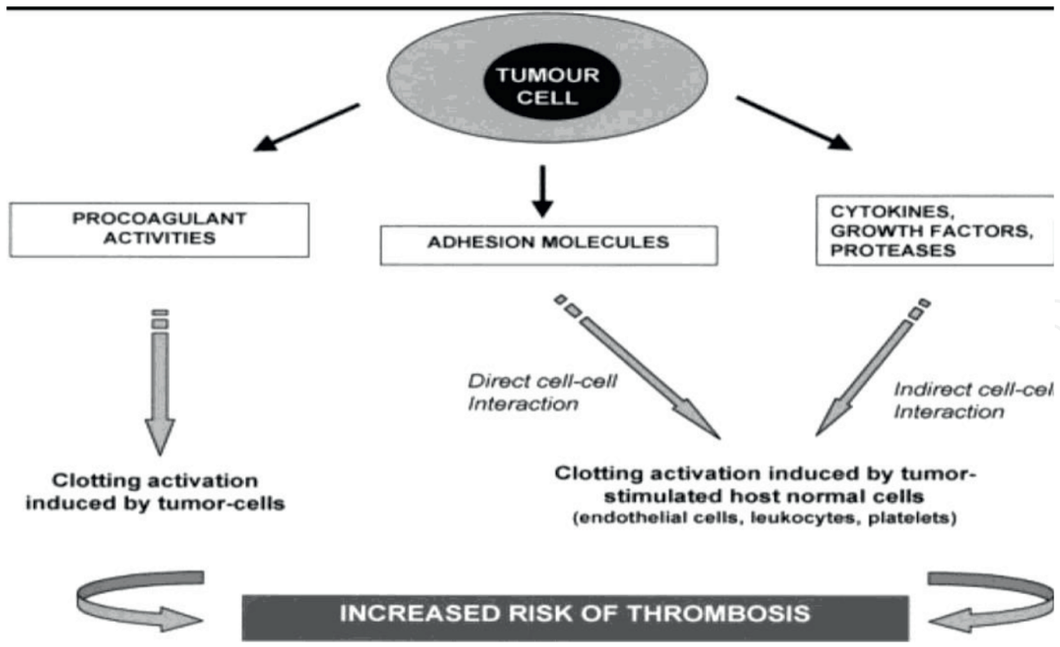


**Figure 1.**
*Hemeostatic system activation by tumor cells [16].*

### 3.2 Indirect mechanism of cancer-associated thrombosis

Indirect mechanism also promotes thrombosis events in cancer patients. Tumoral cells can synthesis and secrete numerous thrombogenic inflammatory cytokines which lead to the expression of specific adhesion molecules on surface of endothelial cells and monocytes, so cause activation of endothelial cells and procoagulant properties [9, 13, 14] (**Figure 1**).

## 4. Prophylaxis of vein thrombotic events in cancer patients

Venous thromboembolism in cancer patients is accompanied with poor prognosis due to complications such as pulmonary embolism or reflecting the advanced stages of cancer as the more important factor. Cancer patients are prone to failure of anticoagulation therapy. Receiving anticoagulant agents can lead to major bleeding two to six times. In contrast, venous thromboembolism (VTE) recurrences occur two to three times in these patients. Thus, primary prevention seems to be more effective way to reduce morbidity and mortality related with thrombotic events in patients with malignancy [17]. However, about 75% of patients do not receive appropriate prophylaxis treatment [18].

### 4.1 Hospitalized cancer patients

Risk of thrombotic events in cancer patients undergoing surgery is as high as 50% which can reduce about 50–80% by thromboprophylaxis agents [17]. Since recent decades, multiples guidelines support the using of venous thromboembolism (VTE) prophylactic drugs in hospitalized active cancer patients unless contraindications which intermittent pneumatic compression or graduated compression stockings are recommended in these cases **Table 1** [14, 19]. Although, it is uncertain if hospital

| | |
|---|---|
| 1. Active uncontrollable bleeding* | 10. Heparin-induced thrombocytopenia (HIT) |
| 2. Active or recent cerebrovascular hemorrhage | 11. Epidural catheter placement |
| 3. Intracranial or intraspinal lesions at high risk for bleeding | 12. Platelet count <50,000/mm$^3$*** |
| 4. Dissection or aneurysm of cerebral vessels | 13. Severe platelet dysfunction |
| 5. Endocarditis, pericarditis | 14. Recent operation at high risk for bleeding |
| 6. Active peptic ulceration | 15. Severe coagulopathy |
| 7. Severe uncontrolled or malignant hypertention | 16. High risk for falling |
| 8. Severe head trauma | 17. Renal impairment |
| 9. Pregnancy** | |

**Active bleeding that requires at least two units of blood products within 24 h.*
***Pregnancy is relative contraindication for warfarin.*
****International Society of Thrombosis and Homeostasis 2014 (ISTH) recommended thromboprophylaxis agents for patients with platelets more than 50,000/mm$^3$, individualize approach in cases with platelets 25,000–49,000/mm$^3$, and against pharmacologic therapy for platelet lesser than 25,000/mm$^3$, [14, 19, 20].*

**Table 1.**
*Relative contraindications for thromboprophylaxis drug in hospitalized cancer patients.*

admission for chemotherapy or bone marrow transplantation displays a risk for venous thromboembolism [20].

American Society of Clinical Oncology 2020 (ASCO) recommended pharmacological thromboprophylaxis for hospitalized cancer patients with acute medical illness, reduced mobility, or undergoing major surgery. However, it should not be advised thromboprophylaxis to patients admitted for minor procedures, chemotherapy infusion, or stem cell/bone marrow transplantation.

Low-molecular-weight heparin (LMWH), fondaparinux, unfractionated heparin (UFH) are proposed prophylaxis drugs by International Society of Thrombosis and Homeostasis 2014 (ISTH), International Initiative on Thrombosis and Cancer 2019 (IITC), and National Comprehensive Cancer Network 2020 [20]. American Society of Hematology 2021 (ASH) guideline recommended low molecular heparin weight (LMHW) over unfractionated heparin (UFH) in hospitalized cancer patients and LMWH or fondaparinux rather than UFH for cancer patients undergoing surgery [21]. They against use of direct oral anticoagulants (DOACs) as prophylactic drugs in these patients [20]. Trials showed the rate of thrombosis has been significantly lower with low-molecular-weight heparin (LMWH) than unfractionated heparin (UFH) without noticeable increase in major bleeding [19].

According to American Society of Clinical Oncology 2020 (ASCO), prophylactic drugs should be commenced preoperatively (one dose 12 hours prior or evening before procedure rather than one dose on the operating table) and continued for at least 7–10 days. Extended prophylaxis with low-molecular-weight heparin (LMWH) is advised up to 4 weeks postoperatively, for high-risk patients undergoing major open or laparascopic abdominal or pelvic cancer surgery [20, 21]. American Society of Hematology 2021 recommended discontinuing thromboprophylaxis at the time of discharge rather than continuing beyond it in hospitalized cancer patients due to medical illness [21].

Non-pharmacological prophylaxis should not be recommended for cancer patients undergoing cancer surgery unless contraindication for using of pharmacological prophylaxis. Combined prophylaxis (pharmacological and mechanical) may be effective for high-risk patients for thrombotic events [20]. American Society of Hematology

2021 (ASH) also suggested pharmacological thromboprophylaxis over combination or mechanical prophylaxis. Although, it recommended mechanical thromboprophylaxis over pharmacological for cancer inpatient undergoing surgery with high bleeding risk. In contrast, early ambulation is over mechanical thromboprophylaxis in post-surgery cancer patients to the opinion of American Society of Hematology Guideline 2021 [21]. International Initiative on Thrombosis and Cancer 2019 (IITC) did not recommend inferior vena cava (IVC) filter for prophylaxis, routinely [20].

### 4.2 Ambulatory cancer patients

Ambulatory cancer patients receiving chemotherapy have increased risk for thromboembolism [20]. Primary prophylaxis decreases the risk of thromboembolism events in these patients, but the related bleeding risk and frequent daily injection have increased [22] and absolute event rate is low in cancer outpatients, too. Thus, thromboprophylaxis is not recommended by guidelines for all ambulatory cancer patients, routinely [20].

Risk stratification can guide selection of ambulatory cancer patient at high risk of venous thromboembolism [23]. Khorana score (KRS) is used as an ideal, simple, and validated risk stratification tool since 2008, to identify patients at risk of venous thromboembolism (VTE) based on clinical and laboratory variables before starting new systematic therapy. It uses platelet and leukocyte counts, hemoglobin level, body mass index, and site of cancer as the predictor for thromboembolism events **Table 2**, [23, 24]. Two randomized trials evaluated the role of anticoagulant agents for primary prevention of venous thromboembolism based on Khorana scoring in outpatients with cancer and demonstrated reduction in incidence of venous thromboembolism [22]. Khorana score seems to be the best known risk stratification tool in recent years which is endorsed by the latest guidelines [23]. Based on Khorana score, score of 0 displays that the patients are at low risk of venous thromboembolism, a score of 1–2 associates with intermediate risk, and a score of ≥3 (maximum score is 6) indicates high-risk patients. This scoring classification relates to symptomatic venous thromboembolism risk of 0.3–1.5%, 1.8–4.8%, and 6.7–12.9% in ambulatory cancer patients under chemotherapy, respectively [25].

Some guidelines suggest Khorana score 3 points or higher as potential indication for anticoagulation but most recommend a threshold of equal and more than 2 points for anticoagulant agent using [22]. Floris T.M. Bosch et al. evaluated thromboprophylaxis effects in ambulatory cancer patients with intermediate risk (2 points) Khorana

| | **Score** |
|---|---|
| 1. Site of cancer: | |
| Very high risk (stomach and pancreatic) | 2 |
| High risk (lung, lymphoma, gynecological, bladder, and testicular) | 1 |
| 2. Pre-chemotherapy platelet count ≥ 350 × $10^9$/L | 1 |
| 3. Pre-chemotherapy hemoglobin level < 100 g/l or use of red cell growth factors | 1 |
| 4. Pre-chemotherapy leukocyte count >11 × $10^9$/L | 1 |
| 5. Body mass index (BMI) ≥ 35 kg/$m^2$ | 1 |
| *Score 0: low risk, score 1–2: intermediate risk, ≥3: high risk.* | |

**Table 2.**
*Khorana score for risk stratification in ambulatory cancer patients [24].*

score, intermediate to high risk (≥2 points) and high risk score (≥3 points) separately, as a systemic review and meta-analysis involving 4626 cancer patients in 2020. They showed significant reduction in venous thromboembolism in intermediate-, intermediate-to-high-, and high-risk patients with no important difference in major bleeding or all-cause mortality. These results explained the indication of thromboprophylaxis for ambulatory cancer patients with intermediate-to-high-risk Khorana score (≥2 points) to reducing the risk of venous thromboembolism [26].

American Society of Clinical Oncology 2020 (ASCO) recommended thromboprophylaxis with apixaban, rivaroxaban, or low-molecular-weight heparin (LMWH) for high-risk outpatients with cancer with Khorana score 2 points and higher, prior to starting a systemic chemotherapy regimen (strength of recommendation: moderate) [20]. Outpatients with multiple myeloma undergoing treatment with immonomodulatory drugs such as thalidomide or linalidomide-based regimens in combination with steroids or systemic chemotherapy drugs are at risk for venous thromboembolism. So, guidelines such as American Society of Clinical Oncology 2020 (ASCO) and International Initiative on Thrombosis and Cancer 2019 (IITC)) recommended low-dose aspirin or low-molecular-weight heparin (LMWH) for these patients as thromboprophylaxis [20]. American Society of Hematology 2021 (ASH) recommended fixed low-dose vitamin K antagonists (VKAs) in these patients, too [21].

## 5. Anticoagulant agents in cancer patients thromboprophylaxis

### 5.1 Aspirin

Platelets activation is a part of coagulation process and venous thrombosis. Aspirin is an inhibitor of platelet-derived cyclooxygenaze1 (COX1) and thromboxane A and is the most common used antiplatelet agents through the world. Studies showed that aspirin can decrease thrombotic events in older patients with cancer without evidence of increased major bleeding [27, 28].

### 5.2 Unfractionated heparin

It is an anticoagulant which activate antithrombin to inhibit clotting enzymes, especially thrombin and factor Xa. Research showed that unfractionated heparin is effective to prevent thromboembolism events in cancer patients. Although, the use of low-molecular-weight heparin (LMWH) is associated with higher reduction in thrombotic events compared to unfractionated heparin in patients with malignancy, especially solid tumor due to increasing of inflammatory component on solid tumor rather than others [27, 29].

### 5.3 Low-molecular-weight heparin (LMHW)

It includes smaller fragments of heparin which activate antithrombin to inhibit thrombin and factor Xa. Inhibition of factor X is more than thrombin compared to unfractionated heparin. Studies demonstrated effectiveness of low-molecular-weight heparin in thrombotic events treatment with low mortality risk in cancer patients. Benefit of it on patient's survival is ambiguous. Although, it is characterized to be associated with reduction in venous thromboembolism as a thromboprophylaxis agent in these patients [27, 30].

Unfractionated heparin is preferred over low-molecular-weight heparin for cancer patients with severe renal impairment (clearance of creatinine less than 30 ml/min) [21].

### 5.4 Funadparinux

It is indirect synthetic analog that binds to antithrombin, thus inhibiting factor Xa and thrombin activation. Fondaparinux is used as anticoagulation agent for venous thrombus or pulmonary emboli. Although, it is mostly used as thromoprophylaxis agent compared to other anticoagulant agents. Megan Taguay et al. evaluated the role of fondaparinux in high-risk patients and demonstrated fondaparinux potential for cancer-associated thrombus refractory to low-molecular-weight heparin and unfractionated heparin. It has bioavailability of 100%, too, and its specificity for antithrombin results in more predictable anticoagulation effects. It is contraindication in patients with clearance of creatinine less than 30 ml/min and should be used with caution in clearance of creatinine between 30 and 50 ml/min [27, 31].

### 5.5 Direct oral anticoagulants (DOACs)

DOACs target thrombin and factor Xa and are more convenient to descript than warfarin [27]. Rivaroxaban and apixaban are the only DOACs using as the primary thromboprophylaxis for ambulatory cancer patients receiving chemotherapy [21]. Studies showed low-dose direct oral anticoagulants (including 2.5 mg twice a day for apixaban and 10 mg once a day for rivaroxaban) can reduce incidence of thrombotic events in high-risk patients with cancer receiving systemic therapy. Rivaroxaban dosage should be reduced in clearance of creatinine more than 15 and less than 50 ml/min. Apixaban dosage should be reduced if age is more than 80 years old and body weight is less than 60 kg and creatinine more than 1.5 g/l [27, 32].

## 6. Conclusion and future horizons

The world's population has been growing, and life expectancy is increasing. The growth of population aging also occurs in parallel with increase in life expectancy [33]. The incidence of most cancers rises with age due to some same mechanisms [34], and old age is a risk factor for cancer-associated thrombosis too, as has been discussed above [8]. Fortunately, early diagnosis and adequate treatment of malignancies result in the improvement of these patients outcome [35]. Although, these therapeutic methods such as some chemotherapy agents or surgery can increase the risk of thrombosis in cancer patients [8, 9]. Despite the life expectancy of cancer survivors has been increased, other illnesses such as cardiovascular disease have developed in these patients [35]. Cancer patients who presented with atrial fibrillation (AF) rhythm or coronary arteries disease have worse outcome including increased thrombotic risk [36]. Thus, thrombotic events risk is a vast issue in cancer patients. It is associated with patients prognosis. Malignancies nature patients-related factors, new therapeutic agents, even improved patients survival, and developing other illnesses or complications in cancer survivors can affect thromboemboli risk in cancer patients. Risk stratification tools and prevention methods are used to evaluate this risk and reduce thrombotic events. Albeit, thromboemboli is still one of the most common causes of death in patients with cancer. Awareness of thromboemboli risk is important for both patients and physicians, and all cancer patients should be educated about symptoms

and signs of thrombotic events. More studies are needed to assess tumor nature and identify new molecular markers as predictor of thrombotic events and help to develop accuracy and specificity of traditional risk stratification tools.

## Abbreviations

| | |
|---|---|
| ADP | adenosine diphosphate |
| AF | atrial fibrillation |
| ASCO | American Society of Clinical Oncology |
| ASH | American Society of Hematology |
| AT | antithrombin |
| ATE | arterial thrombotic event |
| CRS | cytoreductive surgery |
| CVA | cerebrovascular accident |
| DOACs | direct acting dual anticoagulants |
| HIPECH | hyperthermic intraperitoneal chemotherapy |
| HIT | heparin-induced thrombocytopenia |
| IITC | international initiative on thrombosis and cancer |
| ISTH | international society of thrombosis and homeostasis |
| IVC | inferior vena cava |
| KSR | Khorana score |
| LMWH | low-molecular-weight heparin |
| MI | myocardial infarction |
| PAI-1 | plasminogen activator inhibitor-1 |
| PDPN | podoplanin |
| PSM | peritoneal surface malignancy |
| TF | tissue factor |
| UFH | unfractionated heparin |
| VEGFR | vascular endothelial growth factor receptor |
| VKA | vitamin K antagonist |
| VTE | venous thromboembolism |

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## References

[1] Mattiuzzi C, Lippi G. Current cancer epidemiology. Journal of Epidemiology and Global Health. 2019;**9**(4):217-222. DOI: 10.2991/jegh.k.191008.001

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2021;**71**:209-249. DOI: 10.3322/caac.21660

[3] Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, et al. Cancer statistics for the year 2020: An overview. International Journal of Cancer. 2021;**149**:778-789. DOI: 10.1002/ijc.33588

[4] Lichota A, Szewczyk EM, Gwozdzinski K. Factors affecting the formation and treatment of thrombosis by natural and synthetic compounds. International Journal of Molecular Sciences. 2020;**21**(21):7975. DOI: 10.3390/ijms21217975

[5] Ashorobi D, Ameer MA, Fernandez R. Thrombosis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538430

[6] Chernysh IN, Nagaswami C, Kosolapova S, Peshkova AD, Cuker A, Cines DB, et al. The distinctive structure and composition of arterial and venous thrombi and pulmonary emboli. Scientific Reports. 2020;**10**(1):5112. DOI: 10.1038/s41598-020-59526-x

[7] Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. British Journal of Cancer. 2010;**102**(Suppl. 1):S2-S9. DOI: 10.1038/sj.bjc.6605599

[8] Gervaso L, Dave H, Khorana A, et al. Venous and arterial thromboembolism in patients with cancer. JACC: CardioOncology. 2021;**3**(2):173-190. DOI: 10.1016/j.jaccao.2021.03.001

[9] Abdol Razak NB, Jones G, Bhandari M, Berndt MC, Metharom P. Cancer-associated thrombosis: An overview of mechanisms, risk factors, and treatment. Cancers (Basel). 2018;**10**(10):380. DOI: 10.3390/cancers10100380

[10] Dranichnikov P, Mahteme H, Cashin PH, Graf W. Coagulopathy and venous thromboembolic events following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Annals of Surgical Oncology. 2021;**28**(12):7772-7782. DOI: 10.1245/s10434-021-09941-9

[11] Hamza MS, Mousa SA. Cancer-associated thrombosis: Risk factors, molecular mechanisms, future management. Clinical and Applied Thrombosis/Hemostasis. 2020;**26**:1076029620954282. DOI: 10.1177/1076029620954282

[12] Fernandes Caio J, Morinaga LTK, Alves José L, Castro Marcela A, Jardim CD, Carlos VP, et al. Cancer-associated thrombosis: The when, how and why. European Respiratory Review. 2019;**28**(151):180119. DOI: 10.1183/16000617.0119-201. Available from: http://err.ersjournals.com/content/28/151/180119

[13] Piazza G. Venous thromboembolism and cancer. Circulation. 2013;**128**(24):2614-2618. DOI: 10.1161/CIRCULATIONAHA.113.002702

[14] Sheth RA, Niekamp A, Quencer KB, Shamoun F, Knuttinen MG, Naidu S,

et al. Thrombosis in cancer patients: Etiology, incidence, and management. Cardiovascular Diagnosis and Therapy. 2017;**7**(Suppl. 3):S178-S185. DOI: 10.21037/cdt.2017.11.02

[15] Mukai M, Oka T. Mechanism and management of cancer-associated thrombosis. Journal of Cardiology. 2018;**72**(2):89-93. DOI: 10.1016/j.jjcc.2018.02.011

[16] Falanga A, Zacharski L. Deep vein thrombosis in cancer: The scale of the problem and approaches to management. Annals of Oncology. 2005;**16**(5):696-701. DOI: 10.1093/annonc/mdi165 Epub 2005 Mar 31

[17] Brose KM, Lee AY. Cancer-associated thrombosis: Prevention and treatment. Current Oncology. 2008;**15**(Suppl 1):S58-S67. DOI: 10.3747/co.2008.177

[18] Elyamany G, Alzahrani AM, Bukhary E. Cancer-associated thrombosis: An overview. Clinical Medicine Insights. Oncology. 2014;**8**: 129-137. DOI: 10.4137/CMO.S18991

[19] Khorana AA. Cancer and thrombosis: Implications of published guidelines for clinical practice. Annals of Oncology. 2009;**20**(10):1619-1630. DOI: 10.1093/annonc/mdp068

[20] Streiff MB, Abutalib SA, Farge D, Murphy M, Connors JM, Piazza G. Update on guidelines for the management of cancer-associated thrombosis. The Oncologist. 2021;**26**(1):e24-e40. DOI: 10.1002/onco.13596

[21] Lyman GH, Carrier M, Ay C, Di Nisio M, Hicks LK, Khorana AA, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: Prevention and treatment in patients with cancer. Blood Advances. 2021;**5**(4):927-974. DOI: 10.1182/bloodadvances.2020003442

[22] Overvad TF, Ording AG, Nielsen PB, Skjøth F, Albertsen IE, Noble S, et al. Validation of the Khorana score for predicting venous thromboembolism in 40 218 patients with cancer initiating chemotherapy. Blood Advances. 2022;**6**(10):2967-2976. DOI: 10.1182/bloodadvances.2021006484

[23] Mulder FI, Candeloro M, Kamphuisen PW, Di Nisio M, Bossuyt PM, Guman N, et al. CAT-prediction collaborators. The Khorana score for prediction of venous thromboembolism in cancer patients: A systematic review and meta-analysis. Haematologica. 2019;**104**(6):1277-1287. DOI: 10.3324/haematol.2018.209114

[24] Khorana A, et al. Risk Assessment for Cancer-Associated VTE. JACC*:* Asia*.* 2021; 1 (2): 271-273. doi:10.1016/j.jacasi.2021.07.007

[25] Khorana AA, Cohen AT, CarrierM, Meyer G, Pabinger I, Kavan P, et al. Prevention of venous thromboembolism in ambulatory patients with cancer. ESMO Open. 2020;**5**(6);e000948. DOI: 10.1136/esmoopen-2020-000948

[26] Bosch FTM, Mulder FI, Kamphuisen PW, Middeldorp S, Bossuyt PM, Büller HR, et al. Primary thromboprophylaxis in ambulatory cancer patients with a high Khorana score: A systematic review and meta-analysis. Blood Advances. 2020;**4**(20):5215-5225. DOI: 10.1182/bloodadvances.2020003115

[27] Libby P, Bonow R, Mann D, Tomaselli G, Bhatt D, Solomon SD, et al. Braunwald 's Heart Disease. Philadelphia: Elsevier; 2021

[28] Li P, Ning Y, Li M, Li M, Cai P, Siddigui AD, et al. Aspirin is associated with reduced rates of venous thromboembolism in older

patients with cancer. Journal of Cardiovascular Pharmacology and Therapeutics. 2020;**25**(5):456-465. DOI: 10.1177/1074248420925021

[29] Van Matre ET, Reynolds PM, MacLaren R, Mueller SW, Wright GC, Moss B, et al. Evaluation of unfractionated heparin versus low-molecular-weight heparin and fondaparinux for pharmacologic venous thromboembolic prophylaxis in critically ill patients with cancer. Journal of Thrombosis and Haemostasis. 2018;**16**(12):2492-2500. DOI: 10.1111/jth.14317

[30] Zhang N, Lou W, Ji FL, Qiu B, Tsang K, et al. Low molecular weight heparin and cancer survival: Clinical trials and experimental mechanisms. Journal of Cancer Research and Clinical Oncology. 2016;**142**:1807-1816. DOI: 10.1007/s00432-016-2131-6

[31] Tanguay M, Séguin C. Recurrent thrombosis rescued by fondaparinux in high-risk patients: A case series. Research and Practice in Thrombosis and Haemostasis. 2022;**6**:e12773. DOI: 10.1002/rth2.12773

[32] Li A, Kuderer NM, Garcia DA, et al. Direct oral anticoagulant for the prevention of thrombosis in ambulatory patients with cancer: A systematic review and meta-analysis. Journal of Thrombosis and Haemostasis. 2019;**17**:2141-2151. DOI: 10.1111/jth.14613

[33] Gu D, Andreev K, Dupre ME. Major trends in population growth around the world. China CDC Weekly. 2021;**3**(28):604-613. DOI: 10.46234/ccdcw2021.160

[34] White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley SJ. Age and cancer risk: A potentially modifiable relationship. American Journal of Preventive Medicine. 2014;**46**(3 Suppl 1):S7-S15. DOI: 10.1016/j.amepre.2013.10.029

[35] Paterson D, Wiebe N, Cheung W, et al. Incident cardiovascular disease among adults with cancer. JACC: CardioOncology. 2022;**4**(1):85-94. DOI: 10.1016/j.jaccao.2022.01.100

[36] Leiva O, AbdelHameid D, Connors J, et al. Common pathophysiology in cancer, atrial fibrillation, atherosclerosis, and thrombosis. JACC: CardioOncology. 2021;**3**(5):619-634. DOI: 10.1016/j.jaccao.2021.08.011