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Role of four new blood coagulation tests in cancer stem cell-mediated tumor-related venous thromboembolism

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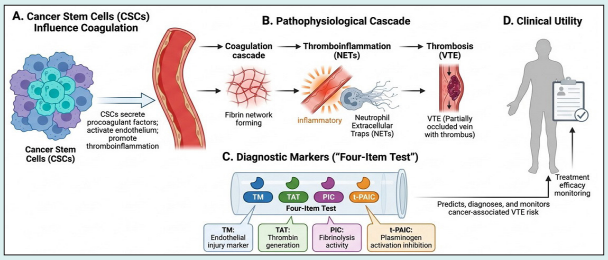
Abstract



Patients with cancer often have a marked hypercoagulable state, which significantly raises the risk of thrombosis. Recent studies have shown that cancer stem cells (CSCs) play a crucial role in creating this prothrombotic environment by influencing the coagulation cascade and triggering thromboinflammation. This review comprehensively examines the role of four novel blood coagulation tests – thrombomodulin (TM), thrombin-antithrombin complex (TAT), plasmin-α2-antiplasmin complex (PIC), and tissue-type plasminogen activator-inhibitor 1 complex (t-PAIC) – in the context of cancer stem cell-mediated tumor-related venous thromboembolism (VTE). These markers offer distinct advantages over traditional coagulation assays for dynamic monitoring of coagulation and fibrinolysis in cancer-associated VTE, providing a more nuanced assessment of patient status. We elucidate the predictive, diagnostic, and risk-assessment value of this "four-item test," exploring its potential to identify patients at high risk of VTE and to monitor treatment efficacy. Furthermore, we delve into the underlying pathophysiological links connecting CSC activity, cancer-associated thrombosis (CAT), thromboinflammation, and the formation of neutrophil extracellular traps (NETs), suggesting that these biomarkers may offer valuable insights into the mechanisms driving thrombosis in cancer.

Introduction

Cancer-associated thrombosis (CAT) refers to venous thromboembolic events occurring in patients with malignancy, including deep vein thrombosis (DVT) and pulmonary embolism (PE). These conditions are the most common manifestations of cancer-related hypercoagulability. As cancer progresses, CAT remains a leading cause of death among patients.[1] It is also associated with decreased survival rates, increased morbidity, higher hospitalization rates, and potential delays or interruptions in systemic therapy.[2] Approximately 20% to 30% of all first-time venous thromboembolism (VTE) episodes are cancer-related.[3] Although advancements in cancer treatment have improved patient outcomes, the risk of VTE has not decreased. In fact, studies suggest that the incidence of CAT has risen over the past two decades,[4,5] with estimates indicating that roughly 15% of cancer patients will experience VTE.[6] Newer systemic therapies, including anti-angiogenic agents, multi-targeted tyrosine kinase inhibitors, immunomodulatory combinations, and immunotherapy, appear to increase the risk of both VTE and arterial thromboembolism. This suggests that CAT is not a problem that diminishes as cancer treatments improve.[7-9]

Patients receiving systemic anticancer therapy exhibit a significantly elevated risk of VTE. Importantly, the risk of CAT is largely influenced by the underlying type of cancer, with pancreatic and gastric cancer (GC), as well as primary brain tumors, demonstrating the highest thrombosis risk.[10] Current venous thrombosis risk prediction models have limited capacity for sub-layering thrombotic events. Several risk prediction models have been developed to identify cancer patients at high risk of VTE, who stand to benefit most from thromboprophylaxis. The Khorana score is currently the recommended clinical model for cancer CAT risk assessment.[11] Despite

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Review Highlights

What is the current knowledge?

- Cancer is linked to a higher incidence of thrombosis, which is more closely associated with CSCs. CSCs exhibit increased procoagulant activity via mechanisms such as TF expression and extracellular vesicle release. However, little is known about the precise function of CSCs and the usefulness of new biomarkers in evaluating this risk.

What is new here?

- This review summarizes the growing body of evidence connecting CSCs to tumor-related VTE. Specifically, we highlight the potential of four new blood coagulation tests—TM, TAT, PIC, and t-PAIC—to measure CSC-driven procoagulant activity, offering a possible avenue for improved risk assessment in cancer patients.

clinical recommendations, the Khorana score has shown suboptimal performance in external validation studies.[12] One reason for this controversy may be that the score was originally designed to identify high-risk outpatients receiving chemotherapy, whereas many validation studies used different inclusion criteria, such as including patients not receiving chemotherapy or different distributions of tumor types. Other limitations include its low positive predictive value and reduced efficacy in specific cancers, such as lung and pancreatic cancer, as the tool was developed for a mixed population of solid tumor patients.[12] A recent large meta-analysis showed that patients with high Khorana scores had only a 1.6-fold higher risk of VTE compared to those with low scores.[13]

Growing evidence suggests that cancer patients exist in a persistent subclinical hypercoagulable state. The processes of fibrin formation and clearance parallel the progression of malignancy, as fibrin and other coagulation products are essential components of both thrombosis and tumor development.[14] The formation and degradation of thrombi result from the interaction of multiple factors within the coagulation, fibrinolysis, inflammatory, and endothelial systems, and several markers can be used to assess these processes.[15] While studies have shown that D-dimer is useful for ruling out thrombosis, it is a degradation product of fibrin clots formed by plasmin.[16,17] Because it appears relatively late in the process, D-dimer offers no advantage for early diagnosis. Therefore, the early diagnosis of VTE is critical for timely treatment, improved prognosis, and better quality of life for cancer patients.

A critical limitation of current risk stratification models is their failure to account for tumor biological heterogeneity, particularly the role of cancer stem cells (CSCs). Emerging evidence suggests that CSCs, which are a specific subset of tumor cells capable of self-renewal, are not only involved in key cancer-related processes such as tumor initiation, metastasis, and resistance to therapy, but they also play a crucial role in promoting a prothrombotic (hypercoagulant) condition within the body. In addition to initiating the angiogenesis process, CSCs can produce a variety of cell phenotypes, including fibroblasts and endothelial cells, which promote tumor development and recurrence by producing and secreting growth factors and extracellular matrix components.[18] Deregulation of tissue factor (TF) expression is one prominent example of the procoagulant characteristics that CSCs and their vascular stroma frequently display.[19] Milsom et al hypothesize that TF plays a role in these interactions either directly or indirectly through procoagulant and signaling effects, the latter of which are carried out in conjunction with juxtaposed protease-activated receptors (namely PAR-1 and PAR-2). Cancer cells, including CSCs and tumor-initiating cells (TICs), may react to plasma proteases (Factors VIIa, Xa, and IIa) and the associated microenvironmental alterations (fibrin deposition, platelet activation) through the TF/PAR system, which functions as a "blood sensing" mechanism.[19]

Consequently, the presence and activity of CSCs may represent a key, yet underappreciated, driver of the persistent hypercoagulable state observed in cancer patients, potentially explaining why some patients with low Khorana scores still develop VTE. The early activation of the coagulation cascade can be predicted by the thrombin-antithrombin complex (TAT), which is extremely sensitive to thrombin production. The plasmin–antiplasmin system is essential for fibrinolysis and blood coagulation. The disintegration of fibrin polymers into soluble fragments is mainly controlled and regulated by plasmin and α2-antiplasmin.[20]

Tissue-type plasminogen activator (t-PA) primarily dissolves fibrin by activating plasminogen and transforming it into plasmin. Following its production, plasmin cleaves t-PA into its 2-chain form through a positive feedback process. This form speeds up the conversion rate and has a 10-fold higher affinity for converting plasminogen into plasmin.[21] A molar excess of its inhibitor, plasminogen activator inhibitor-1 (PAI-1), keeps t-PA inhibited in a typical patent lumen. Plasminogen and t-PA can bind in the presence of fibrin; in the presence of PAI-1, concentration-dependent inhibitory impact is eliminated, and t-PA is brought near enough to cleave plasminogen into active plasmin. The active protease plasmin is produced when an arginine (Arg)- Valine (Val) peptide link inside plasminogen is broken.[22] The t-PA-plasminogen activator inhibitor-1 complex (t-PAIC) is formed when PAI-1 binds with t-PA, indicating the release of t-PA into the bloodstream. Measuring t-PAIC is associated with the level of endothelial damage and aids in evaluating the fibrinolytic system's activation.[23]

Managing CAT can be challenging for clinicians as they must balance the risks of bleeding with the benefits of anticoagulation. Pathologically, VTE arises from imbalances in coagulation, fibrinolysis, and the vascular endothelium.

Given the complexity of CAT, no single factor is enough

for risk assessment (Fig. 1). However, understanding CAT as a thromboinflammatory disease driven by neutrophil extracellular traps (NETs) could lead to better biomarkers. This review evaluates the role of four new blood coagulation tests in cancer stem cell-mediated tumor-related VTE.

Overview of the four novel thrombotic markers

Thrombin-antithrombin complex

In the initial committed stage of the thrombus formation process, prothrombin is activated by proteases to produce thrombin. Thrombin not only catalyzes the development of the thrombus, but also initiates various processes that regulate the flow along the coagulation cascade, both positively and negatively. Therefore, the conversion of prothrombin to thrombin is the only non-redundant stage in the creation of a thrombus, resulting in a crucial coagulation end product.[24] Prothrombin changes into active thrombin when the coagulation system is activated. It is challenging to evaluate directly because thrombin has a very short half-life (seconds) before being neutralized by antithrombin. Instead, a sensitive, indirect indicator of thrombin production and the start of the coagulation cascade is the steady TAT.[25]

Elevated TAT levels indicate a prothrombotic condition and increased thrombin generation, which are crucial for assessing the effectiveness of therapy and predicting the risk of VTE.[26-28] In oncology, thrombin interacts with platelets and endothelial cells to stimulate tumor growth, as well as driving clot formation.[29,30] Studies show that TAT levels are significantly higher in patients with various malignancies—such as lung, head and neck, and colorectal cancers—compared to healthy individuals.[31,32] Clinically, a TAT level > 3.5 ng/mL or > 0.53 ng/mL has been associated with a 6- to 7-fold increase in VTE risk.[33,34] Furthermore, monitoring postoperative TAT is highly effective for identifying patients at high risk for DVT.[27,35]

Thrombomodulin

Thrombomodulin (TM) is a transmembrane glycoprotein on endothelial cells that acts as a key cofactor in the Protein C anticoagulant system. By binding to thrombin, TM shifts its function from promoting clots to activating Protein C, which then inhibits Factors Va and VIIIa.[36,37] TM exists in two forms: a membrane-bound form and a soluble form (sTM) released into the blood after endothelial damage. Therefore, elevated plasma sTM levels serve as a specific marker for vascular endothelial injury.[38,39]

In oncology, TM is expressed not only by endothelial cells but also on the surface of various tumor cells. Elevated plasma TM levels in cancer patients often correlate with disease progression and poor prognosis.[40] Studies in leukemia, for instance, suggest that high plasma TM may result from either tumor cell infiltration or the enzymatic degradation of membrane-bound TM. Interestingly, while high plasma levels indicate an adverse outcome, low expression of TM on the tumor cell surface is linked to increased tumor metastasis and growth.[41] Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1β, can downregulate endothelial TM expression, impair the anticoagulant barrier, and lead to the accumulation of thrombin, which further promotes tumor proliferation through PARs.[42,43]

Consequently, the loss of TM on tumor cells is associated with a higher probability of recurrence, whereas elevated sTM in peripheral blood serves as a specific indicator of vascular endothelial damage.[44,45] Multiple studies have demonstrated that sTM can help rule out VTE and provide early warning for CAT.[46,47] Therefore, monitoring both tumor-surface TM and peripheral sTM levels offers

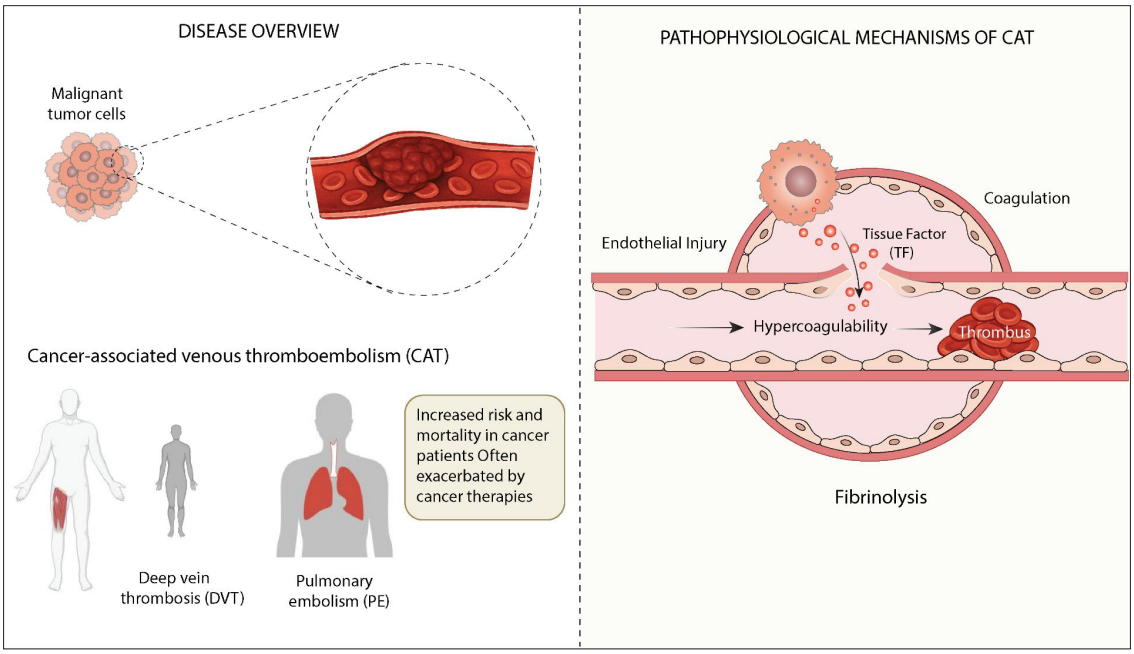

Fig. 1. The main pathophysiological relationships between cancer, vascular endothelium, blood components, and the coagulation system are shown in this schematic overview of cancer-associated thrombosis (CAT).

significant value for diagnosis, efficacy prediction, and long-term prognostic follow-up in cancer patients.

Plasmin-α2-antiplasmin complex

Plasmin-α2-antiplasmin complex (PIC) is a 1:1 complex formed when plasmin is neutralized by α2-antiplasmin. As a core enzyme in fibrinolysis, plasmin dissolves fibrin clots. Since plasmin itself is short-lived and difficult to detect, PIC is used to measure the degree of fibrinolytic activation.[48] Unlike D-dimer, PIC levels are more sensitive to early-stage plasmin activation and are unaffected by anticoagulant drugs.

In patients with hereditary thrombophilia, elevated PIC levels indicate a predisposition to VTE.[49] In the context of malignancy, the balance between coagulation and fibrinolysis is often disrupted, leading to a hypercoagulable state and secondary hyperfibrinolysis. This results in the overproduction of plasmin and, consequently, high PIC expression. While this activation is typically a physiological compensatory response to thrombus formation, it can become dysfunctional in cancer patients. Research indicates that PIC levels are generally higher in cancer patients than in healthy controls, with significantly more pronounced elevations in those with metastasis or comorbid VTE.[50] The combined detection of TAT and PIC yields a diagnostic specificity of 90.91% and a positive predictive value of 89.29% for VTE, serving as an effective early warning indicator for subsequent imaging.[50]

Additionally, PIC has been shown to have a strong predictive value in specific clinical scenarios. In patients with gynecologic malignancy, the Caprini score as well as pre- and post-operative levels of PIC, were found to be predictive of the likelihood of developing VTE following surgery, as determined by univariate logistic regression. The pre-PIC and post-PIC areas under the curve (AUC) were 0.95 and 0.941, respectively.[51]

Ultimately, it was discovered that TAT, TM, PIC, and t-PAIC are crucial in tracking the incidence of perioperative thrombosis in gynecological malignant tumors. Specifically, PIC can serve as the best diagnostic and prognostic marker for venous thrombosis, helping reduce disease incidence and mortality while extending patient survival.

t-PA-PAI-1 complex

t-PA-PAI-1 Complex (t-PAIC) is a complex formed by the 1:1 stoichiometric binding of t-PA and PAI-1. By inhibiting t-PA activity, t-PAIC prevents the conversion of plasminogen into plasmin, thereby hindering the fibrinolytic process.[52] t-PA is a 65 kDa serine protease synthesized primarily by vascular endothelial cells and is released into the bloodstream following endothelial injury. Its primary inhibitor, PAI-1, plays a critical role in suppressing endogenous fibrinolysis and promoting thrombosis.[53] Although active PAI-1 is a potential biomarker for VTE, it is highly unstable in its active conformation, making accurate *in vitro* measurement technically challenging.[54,55] Consequently, t-PAIC is preferred as a stable clinical marker.

The level of t-PAIC typically correlates with total t-PA, PAI-1, and the severity of vascular endothelial damage. During the acute phase of coagulation disorders, t-PAIC provides a more direct and specific reflection of early fibrinolytic activation and the inhibitory capacity of PAI-1. Thus, t-PAIC serves as a dual molecular marker for both endothelial injury and fibrinolytic system activation.[56] In patients with malignant tumors, t-PAIC offers superior diagnostic value for VTE compared to D-dimer. Furthermore, research has linked elevated t-PAIC levels to the frequency of VTE episodes, suggesting that recurrent thrombosis leads to continuous or more intense activation of the fibrinolytic system.[49]

Studies by Yu et al further demonstrate that t-PAIC outperforms D-dimer in terms of sensitivity, specificity, and the AUC.[56] By reducing the false-positive rates often associated with D-dimer, t-PAIC improves the accuracy of VTE identification. Integrating t-PAIC with established clinical tools—such as the COMPASS-CAT, Khorana, and Padua risk scores—can significantly enhance VTE risk prediction. Given its strong correlation with VTE risk in cancers such as breast cancer, t-PAIC should be considered for routine clinical testing to achieve greater diagnostic precision. The graphical representation of the limitations of current risk assessment and management models in CAT is shown in Fig. 2.

Thromboinflammation and neutrophil extracellular traps (NETs)

Thromboinflammation

Thromboinflammation, which involves the combination of clot formation and inflammation, is frequently observed in various human diseases. While it is commonly seen in conditions like superficial thrombophlebitis—where there is inflammation and clotting in the veins—it becomes more severe when it occurs in the small blood vessels of damaged tissues and organs. The core of thromboinflammation lies in the impairment of endothelial cells' ability to prevent clotting and inflammation, resulting in abnormal coagulation processes, complement system activation, platelet activity, and the recruitment of white blood cells within the microvascular system. A-thrombin is essential in regulating both clotting and inflammatory processes, and it has been widely seen as a promising target for treating thromboinflammatory issues.

CAT is fundamentally a thromboinflammatory disorder characterized by a bidirectional relationship between systemic inflammation and thrombotic events. The tumor microenvironment (TME) promotes a pro-inflammatory state by producing C-reactive protein (CRP), which triggers pro-thrombotic variants that drive a self-perpetuating cycle of inflammation and coagulation.[57] Classic thromboinflammation involves the interplay of platelets, leukocytes, and the vascular endothelium.

Neutrophil extracellular traps

Extracellular DNA lattices, known as NETs, are produced

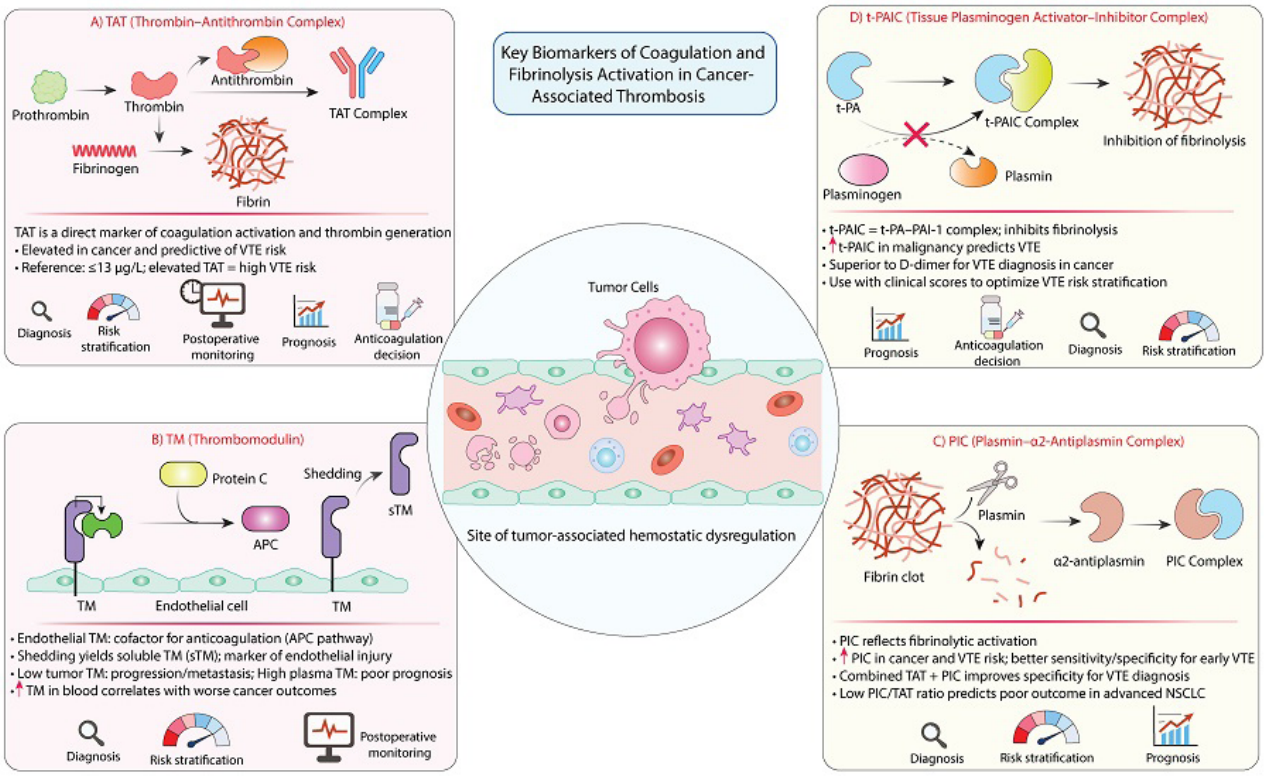

Fig. 2. Key biomarkers of coagulation and fibrinolysis activation in cancer-associated thrombosis: A: TAT (thrombin-antithrombin complex), B: TM (thrombomodulin), C: PIC (plasmin-α2-antiplasmin complex), and D: t-PAIC (t-PA-PAI-1 Complex).

when neutrophils are excessively activated. They are intended to capture pathogens and assist in the fight against infections.[58] NETs are the result of immunothrombosis, which is considered a distinct innate immune process with the specific purpose of limiting the spread of infections in the blood.[58] Notably, the production of NETs in the bloodstream can ensnare more blood cells, leading to the development of pathological thrombus, such as venous thrombosis.

Peptidyl arginine deiminase 4 (PAD4) is necessary for the production of NETs, a process known often known as NETosis, to facilitate histone citrullination. This results in chromatin decondensation and release.[59,60] NETs in ischemic stroke thrombi and surrogate indicators of NETs in ischemic stroke patients' plasma have been discovered in numerous investigations.[61,62] In an inflammatory setting, the endothelium loses its thrombo-resistant qualities and generates chemokines and ILs (such as IL-1β and IL-6) that attract and activate leukocytes.[63] Denorme et al found that platelet-derived high-mobility group box 1 (HMGB1) plays a crucial role in the formation of NETs in the acute phase of stroke, leading to worsened stroke outcomes, using a translational approach studying ischemic stroke patients and using murine models of ischemic stroke.[58] In mice, treatment with a newly identified neonatal NET-inhibitory factor (nNIF) decreased ischemic stroke brain damage and stroke-related death.

In cancer, NETs act as a physical scaffold for platelets and erythrocytes while providing a platform for coagulation activation. According to a study by Yang et al, neutrophils from patients with GC have a higher capacity to release NETs, which stimulate the production of thrombin and subsequently convert fibrinogen into fibrin. Moreover, control neutrophils are stimulated to release NETs in vitro by plasma or platelets obtained from GC patients. Additionally, autonomous NET formation was found to increase and contribute to the hypercoagulable condition in GC patients, while disassembly of the NET structure by DNase I could reduce the procoagulant effect. Furthermore, NET production was strongly associated with levels of TAT and D-dimers, and increased concurrently with the elevation of TNM stage.[64]

Clinical applications of the four thrombotic markers in CAT

Risk prediction and screening

Previous research has identified several clinical and genetic variables that may be linked to the risk of cancer-associated thrombosis. Historically, thrombotic events were only investigated in individuals displaying clinical symptoms such as hemoptysis, chest pain, and swelling in the extremities.[65] Because thrombosis can lead to catastrophic hemorrhagic events, its management is a contentious issue, especially for individuals with lung cancer. Therefore, improving the survival rates of lung cancer patients depends on early detection and prevention of thrombosis.[65]

In order to assess potential risk factors and laboratory indicators, the study by Di et al from 2023 focuses on thrombosis risk factors and identifies high-risk lung cancer patients in the cohort. Within this group, the incidence rate of VTE episodes within six months of a

lung cancer diagnosis was found to be 17.1%, which aligns with previously published results.[66]

A hemostatic imbalance that is typically skewed towards a procoagulant direction and a high frequency of thrombotic consequences are characteristics of malignant disease. The hemostasis systems that play a crucial role in thrombosis are also linked to angiogenesis, metastatic dissemination, and tumor growth. Because the clotting system and cancer are closely related, circulating biomarkers of activation of different hemostasis compartments (such as coagulation, fibrinolysis, platelets, endothelium, and other blood cells) have been thoroughly studied to predict both the thrombotic risk and the outcome of cancer.[67]

It has been demonstrated that thrombin generation, TAT levels, and prothrombin fragment 1 + 2 have the potential to serve as early biomarkers for thromboembolic risk in patients with early-stage primary lung cancer, as well as in patients with localized head and neck cancer.[27]

Combining the four markers with D-dimer and fibrin degradation products (FDP) improves the identification of high-risk individuals in colorectal and cervical malignancies. This enables prompt intervention and better and ultimately leads to better survival rates.[12,68]

Early and differential diagnosis

The coagulation, fibrinolytic, and endothelial systems are all involved in the complex process of thrombosis. Standard laboratory parameters such as D-dimer, FDP, prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, and antithrombin III are used for coagulation testing.[69] However, these indicators are utilized to identify and screen for thrombosis in a later stage and are passively discovered during late thrombosis. They are also insensitive to pre-diffuse intravascular coagulation (pre-DIC) and the pre-thrombotic condition. As a result, these tests might not be able to identify thrombosis early on. There is still a lack of accurate and prompt diagnosis, and thrombolytic therapy monitoring does not provide rapid feedback.[69]

TAT is a sensitive measure of the coagulation system's activation and thrombin generation.[70] Since TAT can rise in the prethrombotic condition, it is best to evaluate anticoagulant medication at this time. As a result, measuring TAT levels is the best way to monitor thrombolytic therapy and make an early diagnosis of thrombophilia. An elevated risk of thrombosis is indicated by a persistent rise in TAT. The fibrinolytic system begins with PIC, which also shows how much the fibrinolytic enzymes have been activated.[71] The indicators PAIC and TM are essential for tracking the fibrinolytic system and endothelial function in patients.[72] While t-PAIC can also shed light on anomalies in the fibrinolytic system and endothelial damage, elevated levels of TM may suggest damage to the vascular endothelium in cancer patients. For diseases like thrombosis and disseminated intravascular coagulation (DIC), these markers are useful in predicting organ failure and clinical outcome.[73] TM and t-PAIC are more sensitive and reliable than conventional coagulation tests when it comes to identifying blood clots in cancer patients, post-surgical thrombosis, and evaluating the efficacy of thrombolysis and endothelial system damage.[73]

In a study by Chanjuan et al, postoperative cancer patients were examined for new biomarkers, such as TM, TAT, PIC, and t-PAI, and the results were compared with D-dimer. The cancer group had significantly higher levels of TAT, TM, and PIC than the control group. Additionally, patients with thrombus cancer had higher levels of these indicators than those without the disease. PIC and TAT demonstrated greater AUC values for thrombosis prediction than D-dimer, according to ROC analysis. In particular, both PIC and TAT were more sensitive than D-dimer in detecting thrombosis in cancer patients, and PIC had a greater specificity than D-dimer.[74] The mentioned indicators are considerably higher in individuals with VTE than in those without, according to research on myeloproliferative neoplasms (MPN) and other solid malignancies. PIC has the best diagnostic effectiveness with an AUC of 0.852.[75]

These markers help with differential diagnosis in addition to clot detection. Levels of TAT, PIC, TM, and t-PAIC are correlated with tumor stage and invasion (Stage III-IV vs. I-II) in gallbladder and gastric malignancies. This aids doctors in differentiating between benign and malignant lesions and evaluating tumor aggressiveness.[35,76]

Prognosis evaluation

CAT is often a marker of advanced or aggressive disease, frequently leading to treatment delays and higher mortality.[77,78] Biomarkers can help track metastasis; for example, TAT and PIC levels are significantly higher in patients with metastatic cancer than in those with localized disease.[50]

Furthermore, specific markers serve as independent predictors of survival. In colorectal cancer, elevated TM and D-dimer correlate with shorter survival times.[79] In advanced non-small cell lung cancer (NSCLC), a low PIC/TAT ratio is a strong indicator of poor prognosis, reflecting a "high-coagulation, low-fibrinolysis" state that promotes tumor progression.[80] Collectively, these biomarkers provide a comprehensive framework for monitoring therapy response and predicting long-term outcomes in cancer patients. The clinical application of the four-marker thrombosis panel in CAT is shown in Fig. 3.

The role of CSCs in coagulation activation

The historical association between malignancy and thrombosis, initially characterized by Virchow, has evolved into a complex understanding of the TME as a hypercoagulable niche. Emerging evidence identifies CSCs not merely as passive contributors, but as master regulators of tumor-associated coagulation. Unlike bulk tumor cells, CSCs possess a distinct procoagulant phenotype driven by specific molecular pathways, including hypoxia-induced

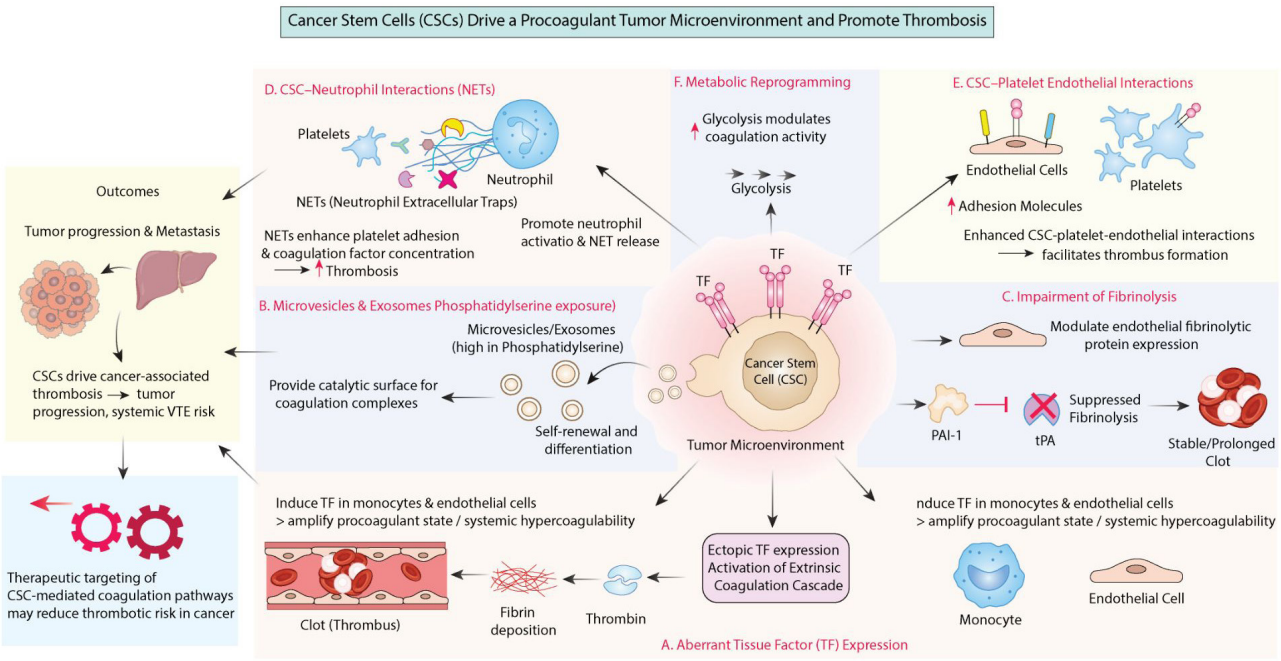

Fig. 3. Combined clinical application of the four-marker thrombosis panel in CAT. Integrated clinical application of the four-marker thrombosis panel for the assessment and characterization of cancer-associated thrombosis (CAT).

signaling and inflammatory crosstalk, which collectively establish a systemic prothrombotic state facilitating metastasis and chemoresistance.[81]

A primary mechanism underlying CSC-mediated coagulation is the aberrant upregulation of TF, the principal initiator of the extrinsic coagulation cascade. In CSCs, TF expression is significantly elevated compared to non-stem tumor cells, primarily driven by the stabilization of hypoxia-inducible factor-1α (HIF-1α) under hypoxic conditions and activation of the nuclear factor-kappa B (NF-κB) pathway by inflammatory cytokines such as TNF-α and IL-6.[82] This ectopic TF expression on the CSC surface exposes phosphatidylserine residues, creating a catalytic platform for TF-FVIIa complex assembly. This complex directly activates Factor X and IX, leading to the burst generation of thrombin. Furthermore, CSC-derived exosomes and macrovesicles are enriched in TF and Annexin V, which shield the negatively charged phospholipid surface from anticoagulant proteins such as antithrombin, thereby amplifying thrombin generation and promoting fibrin deposition locally within the tumor vasculature.

Beyond the initiation of coagulation, CSCs critically disrupt the hemostatic balance by suppressing fibrinolysis. CSCs secrete high levels of (PAI-1), which inhibits both t-PA and urokinase plasminogen activator (u-PA).[83] This inhibition prevents the conversion of plasminogen to plasmin, the key enzyme responsible for fibrin degradation. Consequently, the half-life of fibrin clots is significantly prolonged, stabilizing thrombi that may serve as physical conduits for circulating tumor cells (CTCs). Additionally, CSCs have been shown to upregulate thrombin-activatable fibrinolysis inhibitor (TAFI) expression in endothelial cells via paracrine signaling, further impairing the endothelial capacity to resolve clots.

The molecular crosstalk between CSCs and neutrophils within the TME constitutes a critical driver of NET formation, a sophisticated immune-evasion mechanism that significantly contributes to tumor progression, metastasis, and therapeutic resistance. This intricate biological interaction begins with the unique secretory profile of CSCs, which are a subpopulation of tumor cells possessing stem-like properties such as self-renewal, plasticity, and inherent resistance to apoptosis. To sustain their survival and proliferative potential in the harsh, hypoxic, and nutrient-poor conditions of the TME, CSCs secrete high levels of the pro-inflammatory chemokine C-X-C motif chemokine ligand 8 (CXCL8), also known as IL-8.[84] CXCL8 serves a dual, synergistic purpose in this context: first, it acts as a potent chemoattractant by binding to its receptors, C-X-C motif chemokine receptor 1 (CXCR1) and C-X-C motif chemokine receptor 2 (CXCR2), on the surface of circulating neutrophils, thereby drawing these innate immune cells from the bloodstream into the tumor niche.[85] Second, and perhaps more critically, CXCL8 induces a state of "priming" in these recruited neutrophils. Priming is a transient state of partial activation where neutrophils undergo metabolic reprogramming and upregulate the expression of various surface receptors, including integrins and Fc receptors. This process lowers the activation threshold of the neutrophils, making them hypersensitive to subsequent stimuli and preparing them for a rapid and robust effector response.

However, recruitment and priming alone are often insufficient to trigger the explosive release of NETs, which requires a strong secondary signal. This secondary trigger is provided by damage-associated molecular patterns (DAMPs), particularly HMGB1, which are released in large quantities by stressed, injured, or dying

CSCs within the TME. As tumor cells undergo metabolic stress or therapy-induced cell death, they passively release HMGB1, a nuclear protein that functions as an alarmin or danger signal in the extracellular space.[86] Once released, HMGB1 interacts specifically with pattern recognition receptors on the surface of the already-primed neutrophils, primarily Toll-like Receptor 4 (TLR4) and the receptor for advanced glycation end-products (RAGE).[87] This interaction initiates a powerful intracellular signaling cascade, involving pathways such as NF-κB, mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase/Akt (PI3K/Akt), which converges on the regulation of oxidative burst and chromatin decondensation. Because neutrophils have already been primed by CXCL8, the signal from HMGB1 is significantly amplified, pushing the cells past the point of no return. This synergistic signaling network culminates in NETosis, a specialized form of cell death in which the neutrophil's nuclear envelope breaks down, histones become citrullinated, and chromatin decondenses, mixing with granular proteins that are then expelled from the cell as extracellular fibers.

The outcome of this synergistic signaling network is the formation of a dense, fibrous meshwork of DNA, histones, and antimicrobial proteins—known as NETs—specifically within the CSC-rich niche. Rather than serving their traditional role in pathogen defense, these NETs in the TME assume a pathological function by creating a physical and biochemical shield around the CSCs. This extracellular matrix acts as a barrier that traps chemotherapeutic drugs, preventing them from penetrating deep into the tumor core and reaching the nuclear targets of the CSCs. Furthermore, the sticky nature of NETs can facilitate the adhesion and survival of CTCs, promoting metastasis.[88] By shielding the CSCs from both cytotoxic drugs and immune surveillance, the NETs ensure the survival of the most aggressive and therapy-resistant subpopulation of tumor cells. Consequently, this protective mechanism confers profound chemoresistance, allowing the tumor to survive initial treatment and eventually leading to disease recurrence and metastasis. Thus, the NETosis-mediated CSC-neutrophil axis represents a pivotal immune-evasion strategy that tumors exploit to ensure their long-term persistence and therapeutic failure.

Emerging evidence suggests that the procoagulant properties of CSCs are not solely attributable to the release of procoagulant factors, but also to alterations in their own cellular structure and function. CSCs exhibit increased expression of adhesion molecules, facilitating interactions with platelets and endothelial cells, thereby enhancing thrombus formation. Furthermore, alterations in CSC metabolism, such as increased glycolysis, can influence the coagulation cascade. Understanding these complex interactions is crucial for developing targeted therapies aimed at mitigating the prothrombotic risk associated with CSCs and improving outcomes for cancer patients. Future research should focus on identifying specific molecular targets within CSCs that regulate coagulation activation, paving the way for novel antithrombotic strategies tailored to the unique biology of these cells.

Conclusion

The four novel thrombotic markers—TAT, PIC, TM, and t-PAIC—represent valuable indicators of endothelial damage and coagulation dysfunction, particularly within the context of CSC-mediated tumor-related VTE. Their combined detection offers a sensitive, non-invasive approach for identifying thrombosis in cancer patients, with potentially superior accuracy compared to single-marker assays. This integrated diagnostic framework improves risk stratification and prognostic evaluation, guiding clinicians toward timely thromboprophylaxis and more effective treatment strategies. Recent advances highlighting the role of NETs in CAT further underscore the complex interplay driving these procoagulant events, potentially influenced by CSC activity.

However, while promising, the clinical application of this four-item test faces challenges related to diagnostic specificity and the need for standardized reference ranges, particularly considering the heterogeneity of cancer types and treatment regimens. Future research should prioritize large-scale, multicenter prospective studies to establish individualized reference intervals tailored to specific tumor types and treatment protocols, while also investigating the correlation between biomarker levels and CSC characteristics. Integrating traditional thrombotic markers with NET-specific indicators and advanced imaging modalities will facilitate the development of robust, multidimensional diagnostic models, ultimately providing a more precise biological foundation for the prevention and management of CAT driven by CSCs.

Authors' Contribution

Conceptualization: Nina Zhou.
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Writing–original draft: Nina Zhou, Sai Chen.
Writing–review & editing: Sai Chen.

Competing Interests

None to be declared.

Declaration of AI-Assisted Tools in the Writing Procedure

The authors confirm that artificial intelligence (AI) was not used in the creation of any figures or the graphical abstract included in the manuscript. All figures were created using Adobe Illustrator.

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