Cancer-associated thrombosis: limitations of conventional models and advances with endothelial cell-based microfluidics incorporating thrombin generation

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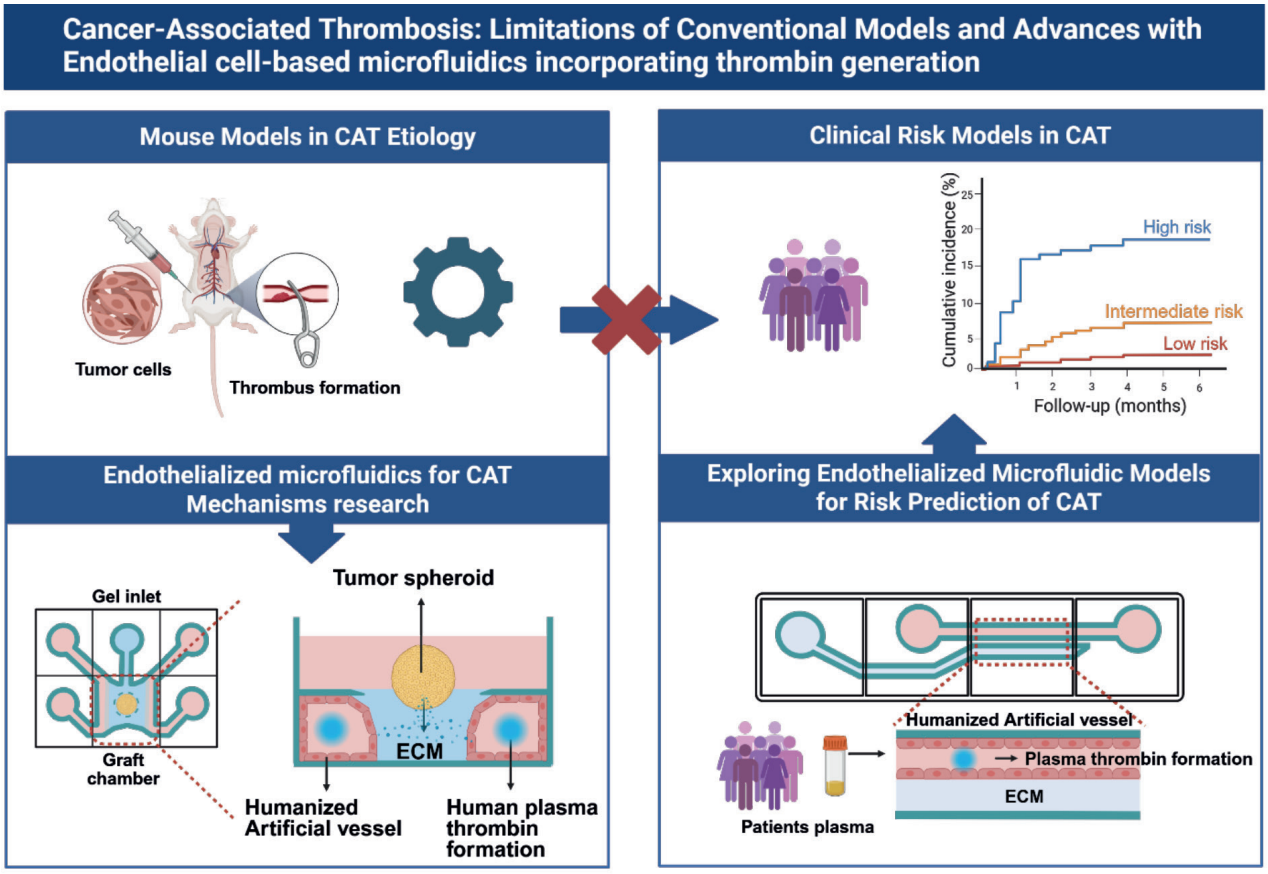
ABSTRACT

Apart from cancer progression itself, cancer-associated thrombosis (CAT) is the second leading cause of death among cancer patients. However, the mechanisms underlying CAT remain incompletely understood. Traditional animal models cannot fully reproduce the complex pathophysiological process of CAT in humans. Meanwhile, existing clinical prediction models are still insufficient to provide reliable risk prediction tools for venous thromboembolism (VTE) in cancer patients. With the accelerating development of microfluidics technology, it has become possible to construct thrombotic microenvironments with high physiological relevance *in vitro*, providing a new platform for the study of CAT. In this review, we summarized the contributions and limitations of animal models and clinical studies to CAT, and highlighted a series of artificial vascular microfluidics developed by our research group in recent years that can, to some extent, simulate the *in vivo* microenvironment for CAT. Based on this microfluidics platform, we conducted thrombin generation analysis to explore the potential mechanisms of cancer-related thrombosis and predict VTE risk in cancer patients. Finally, we further discuss the key issues and the challenges in the future.

Key words: cancer-associated thrombosis (CAT); venous thromboembolism (VTE); microfluidics; artificial vessel; thrombin generation assay; animal models; clinical prediction models.

GRAPHICAL ABSTRACT



Key words: cancer-associated thrombosis (CAT); venous thromboembolism (VTE); microfluidics; artificial vessel; thrombin generation assay; animal models; clinical prediction models.

Introduction

Thrombosis is an important complication of cancer.[1] Compared with the general population, patients with malignant neoplasms have an approximately 4-7-fold higher risk of venous thromboembolism (VTE).[2] Antitumor treatment such as chemotherapy, targeted anti-cancer therapies and immunotherapy, can further increase the risk of VTE.[3-5] Cancer patients with thrombosis often experience reduced quality of life and shorter survival.[6] Furthermore, cancer patients with VTE bear a greater economic burden, with overall health care costs in the United States estimated to be about 1.7-1.8 times higher than cancer patients without VTE.[2] Therefore, investigating the mechanisms of cancer-associated thrombosis (CAT) is crucial for improving thrombosis risk prediction and for guiding the development of more effective therapeutic strategies.

However, due to the complexity of the mechanisms underlying CAT, ideal biomarkers are still lacking. As a consequence, existing clinical prediction models have limited predictive capacity. Furthermore animal models used to test the causality of these biomarkers fail to faithfully reproduce the process of CAT in humans.[7,8] Therefore, there is a need for detection methods and research models with greater physiological relevance. Due to advances in microfluidic technology, it has become possible to establish models of CAT in microfluidic platforms.[9] First, the controllable flow conditions can reproduce the hemodynamic shear environment of human blood flow, while the flexible cellular composition and perfusion systems enable the investigation of the roles of different cancer cell types and various coagulation components in the process of CAT. Measuring the procoagulant state has always been crucial in CAT research. Traditional coagulation tests such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) cannot assess hypercoagulability of cancer patients;[10,11] compared to these traditional coagulation tests, which are limited to the early stages of coagulation from initiation to fibrin formation, the thrombin generation assay is a global coagulation assay. It enables dynamic measurement of thrombin generation, including the velocity index, peak thrombin levels, endogenous thrombin potential (ETP), and inhibition phase. It captures the entire coagulation process in the sample, encompassing initiation, amplification, and termination. Therefore, it reflects not only the overall coagulation potential of the sample but also the balance between procoagulant and anticoagulant processes. Our laboratory has developed a series of microfluidic chip models to simulate CAT and has integrated them with the thrombin generation assay to explore the potential application of mechanistic insights and related parameters in the development of clinical prediction models.[12-14] In this review, we discuss the development and limitations of animal models and clinical risk prediction models in research on CAT and highlight the application of thrombin generation assay based on the microfluidic chip platform independently developed in our laboratory in this field.

Mouse models for investigating the etiology of CAT

In studies of CAT, mouse models are not only used to recapitulate the hemodynamic features of thrombus formation, but they also play an indispensable role in systematically elucidating the complex cellular and molecular mechanisms underlying this process. In a model established by inducing venous blood flow restriction in mice, approximately 80% reduction of blood flow was achieved without disrupting the vascular endothelium, thereby mimicking the low shear rate clinical conditions characteristic of human deep vein thrombosis.[15] The study demonstrated that blood flow restriction leads to the accumulation of leukocytes, such as monocytes and neutrophils, along the venous wall.[15] Tissue factor (TF) derived from leukocytes activates the extrinsic coagulation pathway, resulting in fibrin formation, which is the main component of VTE.[15] Neutrophils within the thrombus further promote thrombus propagation by binding factor XII (FXII) and forming neutrophil extracellular traps (NETs).[15] In this process, platelets interact with immune cells via Glycoprotein Ibα (GPIbα), facilitating leukocyte recruitment and enhancing neutrophil dependent coagulation, thereby driving thrombus growth and stabilization.[15]

When tumors are induced in the mouse model of venous thrombosis, tumor-derived extracellular vesicles (EVs), particularly those expressing TF, play a critical role in the pathogenesis of CAT.[16-18] Animal studies have demonstrated that TF positive EVs derived from human pancreatic cancer cell lines can activate platelets and induce platelet aggregation in a thrombin-dependent manner, leading to increased thrombus formation and this prothrombotic effect can be attenuated by anti-human TF antibodies or clopidogrel treatment. However, the clinical relevance of circulating TF positive EVs in predicting VTE remains controversial. Although studies have shown that elevated TF positive EVs are associated with an increased risk of VTE in pancreatic cancer patients.[16,19] In other cancers, the contribution of TF positive EVs to VTE remains unclear.[20] In brain and ovarian cancers, podoplanin (PDPN) EVs interact with platelet CLEC-2 to induce platelet ag-

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gregation and promote thrombus formation.[21-23] Notably, PDPN in combination with IDH1 mutation has been identified as one of the strongest predictors of VTE in patients with gliomas,[24] highlighting that distinct tumor types may drive thrombosis through different molecular pathways. Tumors can reprogram stromal macrophages via CXCL13, inducing the release of small extracellular vesicles (sEVs) enriched with clustered integrin β2, which interact with platelet glycoprotein Ib (GPIb) and thereby trigger platelet aggregation.[25]

Tumor cells can also release granulocyte colony-stimulating factor (G-CSF) and proinflammatory mediators such as platelet-activating factor (PAF) and interleukin 8 (IL-8).[26,27] These factors induce neutrophilia and prime neutrophils into a pre-activated state, thereby facilitating the formation of NETs and promoting thrombosis.[28] NETs are composed of DNA, citrullinated histone H3 (H3Cit), and neutrophil granule proteins, and their main function is to capture and restrict pathogens.[29] However, intravascular NETs can also act as scaffolds[30] that promote platelet adhesion, fibrin deposition, and enhance tissue factor and factor XII dependent coagulation, thereby significantly promoting thrombus formation.[31-33]

Various tumor-bearing mouse models, such as breast cancer, melanoma, and pancreatic CAT models, have demonstrated a critical role for platelets in cancer-associated thrombosis (CAT).[34] Specifically, breast cancer bearing mice with antithrombin down-regulation display hypercoagulability and increased platelet counts.[35] In melanoma mouse models, platelets exhibit enhanced motility and accelerate thrombus formation.[36] In addition, tumors can secrete adenosine diphosphate (ADP), which activates platelets *via* P2Y1 and P2Y12 receptors to promote thrombosis, and inhibition of P2Y12 reduces this prothrombotic effect in pancreatic cancer models.[37,38] Tumor-derived EVs, platelet activation, and dynamic interactions between tumor, immune system, and platelets have been shown to be important mechanisms driving the occurrence and progression of CAT in various mouse models.

However, it should be noted that although mouse models have irreplaceable value in mechanistic studies, the clinical translatability of findings derived from mouse models remains limited. Mouse models can be broadly classified into two categories. The first category comprises immunocompetent mouse models, which can only support murine tumors such as 4T1, LLC, and PanC02. Although these models possess an intact immune system, murine tumors do not fully recapitulate the biological characteristics of human tumors. The second category includes immunodeficient mouse models that allow for the transplantation and growth of human derived tumors. However, the lack of a functional immune system represents a major limitation for investigating the contribution of the immune system. In addition, one of the most commonly used murine models to study thrombosis either in the context of cancer or in a general thrombosis context, is the inferior vena cava ligation (IVC-L) model.[39] This model induces thrombosis by completely blocking blood flow and is characterized by high stability and reproducibility.[39] However, because blood flow is entirely interrupted, it is difficult to realistically simulate the non-invasive, naturally occurring CAT process in humans, and it also limits the evaluation of the antithrombotic drug efficacy.[40] The inferior vena cava stenosis (IVC-S) model, which slows blood flow through incomplete ligation and induces thrombus formation without endothelial injury, is closer to the physiological process of CAT. However, thrombus size can vary considerably, which may be explained by handling or animal-specific characteristics.[41,42] Ferric chloride models and Rose Bengal/laser-induced models, which rely on thrombosis induction by exposing the blood vessel to chemical substances or laser-induced endothelial injury are easy to operate and have a high success rate, but they primarily reflect injury induced thrombosis rather than CAT.[27,42] Non-invasive mouse CAT models have been developed through tumor transplantation combined with modulation of the anticoagulant system to induce a hypercoagulable state.[35] However, there are fundamental physiological differences between mice and humans in terms of platelet size and count, thrombin receptor type and the function of coagulation factors.[43-48]

These physiological differences may lead to species-specific bias in the prothrombotic mechanisms and responses to antithrombotic therapy.[47] Last, but not least, all of these models rely on surgical manipulation, potentially creating artifacts. For these reasons, although murine models have revealed substantial mechanistic insights, the translational success of preclinical findings remains limited, thus it is necessary to develop models that closely recapitulate the characteristics of human CAT.

Mechanistic studies of CAT using thrombin generation assay in endothelialized microfluidic systems

Microfluidic technology has been gradually introduced into the studies on the mechanism of CAT, providing a new experimental platform for elucidating the dynamic interactions among tumors, the vasculature, and the coagulation system.[49] Compared with traditional in vitro models, this type of model can more faithfully recapitulate thrombus formation within the tumor microenvironment by incorporating three-dimensional architecture, an intact endothelial barrier, and physiologically relevant microfluidic conditions.[49] Importantly, integrating thrombin generation assay into microfluidic chips enables real-time and quantitative monitoring of thrombin formation under controlled flow, capturing both the initiation, propagation and suppression phases of thrombin generation.[50] Thrombin is a central regulator of hemostasis that exerts both procoagulant and anticoagulant functions, including fibrin formation, platelet activation, and anticoagulation to maintain the balance of the coagulation system.[51] This method can provide a more physiologically relevant assessment of hypercoagulable states and treatment response in CAT.[12]

Our previous RNA sequencing analysis of colorectal cancer (CRC) samples with and without VTE showed that the regenerating islet-derived family, member 4 (REG4), is one of the most significantly differentially expressed genes in tumors from patients with VTE.[52] We further performed immunohistochemical staining on tumor samples from the same CRC patient cohort to detect REG4 expression and found that the combined protein expression of REG4 and A1AT showed the strongest association with CAT.[14] We systematically validated the function of the candidate molecule REG4 in colorectal cancer CAT by establishing a perfusable artificial blood vessel platform, using a OrganoPlate 2-lane system and human umbilical vein endothelial cells (HUVECs) (Figure1a).[53] Subsequently, the artificial vessels were co-cultured with the conditioned media of wild-type RKO colorectal cancer cells, mock transfected RKO cells, or REG4 overexpressing RKO cells. Normal pool plasma (NPP) was then

perfused into the system to perform a thrombin generation assay, and thrombin activity was quantitatively monitored using an automated fluorescent imaging system. In this microfluidic hypercoagulable model, conditioned media from REG4-overexpressing RKO cells did not significantly enhance thrombin generation. This observation is consistent with the results obtained from standard coagulation assays performed in NPP in the presence of recombinant REG4, including prothrombin time (PT) and activated partial thromboplastin time (aPTT). In contrast, stimulation with TNF-α, used as a positive control, induced a marked increase in thrombin generation, thereby confirming the sensitivity and dynamic range of this assay. In general, these results indicate that although REG4 expression shows an association with VTE in patients with colorectal cancer, it does not have a direct functional effect on endothelial related thrombin generation under microfluidic conditions. Even in the absence of clear mechanistic evidence, REG4 may still have value as a predictive biomarker for VTE risk in colorectal cancer. In this study, we used RKO as the experimental cell line for colorectal cancer. Its molecular characteristics, including wild-type TP53 and BRAF mutations, may not fully reflect the heterogeneity of advanced colorectal cancer.[54] This highlights the importance of faithfully reproducing patient-derived tumor heterogeneity in research. Therefore, integrating patient-derived colorectal cancer organoids into microfluidic systems may provide a more physiologically relevant platform for further research into CAT mechanisms. This study highlights the importance of performing functional validation using physiologically relevant microfluidics platforms to identify true mechanistic drivers of CAT.

We also investigated the mechanisms underlying glioblastoma-associated thrombosis in similar models.[12] We constructed a microfluidic chip co-culture system using Mimetas OrganoPlate Graft models that integrate two artificial blood vessels formed from HUVECs with a TF overexpressing U-251 glioblastoma cell line-based tumor compartment (Figure1b). By integrating a thrombin generation assay (TGA) within the microfluidic chip, we demonstrated that tumor cell-derived TF markedly enhances the procoagulant state of plasma. Compared to the control group, TF overexpressing tumor spheroids resulted in a significant increase in ETP. This effect was markedly reversed by the FXa inhibitor rivaroxaban or a TF blocking antibody, demonstrating that TF overexpressed U-251 cells exhibited a procoagulant effect. It also shows the potential application of microfluidic chips in the screening and mechanism verification of anticoagulant drugs.

In summary, these two studies demonstrate that microfluidic chips based functional coagulation analysis can not only validate known procoagulant pathways, such as TF initiated coagulation activation but also verify the roles of potential other tumor-expressed procoagulant factors in CAT, thereby improving the robustness of mechanistic investigations. By integrating endothelial and tumor interactions, flow conditions, and coagulation function assay, making experiments more controllable and more representative of human biology, and thereby partially overcoming the limitations of traditional animal models.

Clinical risk models for CAT

Despite significant advances in understanding the biological mechanisms underlying CAT, the clinical management of CAT relies on accurate risk stratification.[1] Patients with cancer exhibit marked heterogeneity in thrombotic risk depending on tumor type, stage, treatment.[55] To identify the population at highest risk of venous thromboembolism for prevention and treatment, various clinical risk models of CAT have been developed and validated, such as the Khorana score, Vienna CATS, PROTECHT, CONKO, COMPASS-CAT, ONKOTEV, ThroLy, and TiC-Onco (Table 1). However, multiple multinational, prospective, and externally validated studies have consistently shown that these models have limited predictive ability in real-world clinical scenarios.[56]

The Khorana score is currently the only CAT risk assessment tool widely recognized by international clinical guidelines. Its main advantage is that all variables are derived from routine clinical in-

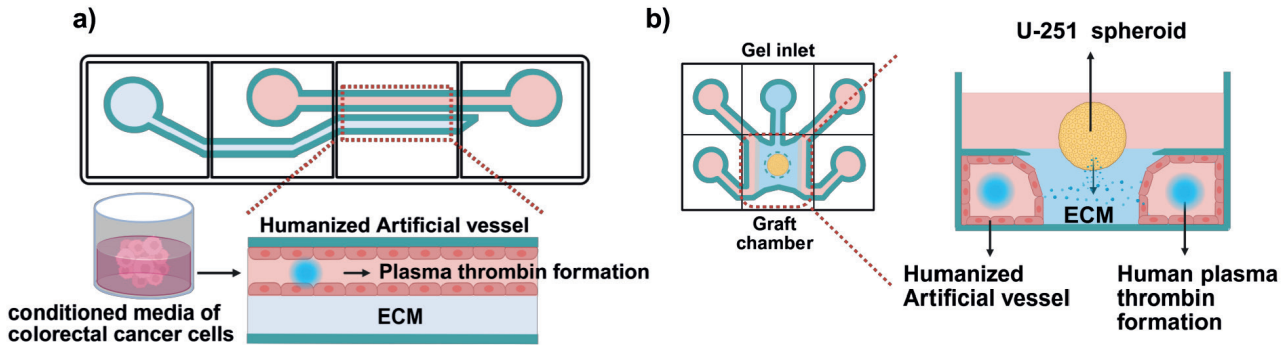

Figure 1. Schematic of the chip model used in a CAT etiology study. a) Overview of the OrganoPlate 2-lane system. Conditioned medium derived from colorectal cancer cells was introduced into the artificial vessel formed by HUVECs and co-culture for 4 h. The medium was then removed, and normal pooled plasma was perfused for the thrombin generation assay, and thrombin formation was measured by fluorescence intensity. b) Overview of the OrganoPlate Graft system. The device contains gel inlets for collagen loading, forming the ECM compartment around the artificial vessel. A U251 spheroid was seeded in the graft chamber. The artificial vessel, formed by HUVECs, was co-cultured within the system to enable tumor-vascular interaction. Tumor-derived procoagulant factors released from the spheroid directly acted on the endothelialized vessel, thereby modulating thrombin generation within the artificial vessel.

Table 1. Summary of clinical risk scores for cancer-associated thrombosis.

Model	Patients population	Predictive variables	Predictive performance	Validation in other cohorts
Khorana score[65]	Breast, lung, ovarian, sarcoma, colon, and lymphomas cancers Derivation cohort, n=2701 Validation cohort, n=1365	Site of cancer (2 points for very high-risk site, 1 point for high-risk site); Platelet count of 350 x 10^9/L or more; Hemoglobin less than 100 g/L (10 g/dL) and/or use of erythropoiesis-stimulating agents; Leukocyte count more than 11 x 10^9/L Body mass index of 35 kg/m^2 or more (1 point each)	Over a median of 2.5 months Derivation cohort: 7.1% in high-risk (score >/=3) category (C-statistic =0.7) Validation cohort: 6.7% in high-risk (score >/=3) category (C-statistic =0.7)	6-month VTE incidence prediction, n=876AUC=0.52 (95% CI 0.47-0.58)[56] Vienna CATS cohorts: the hazard ratio (HR) of VTE was 2.1 (95% CI: 1.6-2.6) per 1 point increase in the risk score (2010)[57]
Vienna CATS score[57]	Brain, breast, lung, stomach, colorectal, pancreas, kidney, prostate, and hematologic malignancies (myeloma and lymphoma), n=819	Khorana scoresoluble P-selectin ≥53.1 ng/mL D-Dimer ≥1.44 µg/mL	Predictive values for VTE at 6 months Univariable Cox HR per 1-point increase: 1.8 (95% CI 1.5–2.2)	6-month VTE incidence prediction, Vienna CATS score n=876 AUC=0.57 (95% CI 0.48-0.66) (2017)[56]
PROTECHT[66]	Lung, gastrointestinal (stomach, colon, or rectum), pancreatic, breast, ovarian, or head and neck cancer, n=378	Khorana score Cisplatin/carboplatin or gemcitabine (1 point) Cisplatin/carboplatin or gemcitabine combination (2 points)	PROTECHT score identified 32.8% of patients as high risk, capturing 66.7% of VTE events	6-month VTE incidence prediction, n=876 AUC=0.59 (95% CI 0.52-0.66) 56 n=117 In NSCLC cohort c-index 0.51-0.59[67]
CONKO score[60]	Pancreatic cancer, n=312	Site of cancer (2 points for very high-risk site, 1 point for high-risk site) Platelet count of 350 x 10^9/L or more Hemoglobin less than 100 g/L (10 g/dL) and/or use of erythropoiesis-stimulating agents Leukocyte count more than 11 x 10^9/LWHO performance status >=2	3-month incidence of venous thromboembolism Higher WHO performance status associated with increased VTE risk; 3-months VTE incidence ~10% in high-risk group (≥3)	n=876 AUC=0.50 (95% CI 0.44-0.57) (2017)[56]
ThroLy score[68]	Non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) Derivation cohort, n=1236 Validation cohort, n=584	Previous venous and/or arterial events, mediastinal involvement BMI >30 kg/m^2 Reduced mobility Extranodal localization Development of neutropenia Hemoglobin level <100g/L	Derivation cohort, positive predictive value (PPV): Validation cohort, PPV: 28.9% (95% CI 19.1-40.5%)	n=428 High-risk group: 38.9% developed VTE C statistic-0.55 (2018)[69]
COMPASS-CAT[70]	Breast, colorectal, lung, and ovarian cancers, n=1023	Anthracycline or anti-hormonal therapy Time since cancer diagnosis ≤6 months Central venous catheter Advanced stage of cancer Presence of cardiovascular risk factors Recent hospitalization for acute medical illness Personal history of VTE Platelet count 350×10^9/L	At 6 monthsVTE incidence in the high-risk group: 13.3% The area under the curve of receiver operating characteristics analysis was 0.85	n=3814 AUC=0.62[61]

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Table 1. Continued from previous page.

Model	Patients population	Predictive variables	Predictive performance	Validation in other cohorts
ONKOTEV score[58]	Breast cancer, Gastroenteropancreatic cancers, genitourinary tract cancers, lung cancer, other, n=843	Khorana score >2 Previous venous thromboembolism Metastatic disease Vascular/lymphatic macroscopic compression	Time-dependent AUC=0.72 (3 months), 0.75 (6 months), and 0.70 (12 months)	n=425 Time-dependent AUC=0.70 (95% CI 0.62–0.79) at 3 months, 0.73 (95% CI 0.66-0.79) at 6 months, and 0.72 (95% CI 0.65-0.77) at 12 months[62]
Vienna CATS/MICA[71]	Derivation cohort, CATS n=1423 Validation cohort, MICA n=832	Tumor-site category D-dimer	At 6 monthsc-index 0.66 (CATS); 0.68 (MICA)	-
TiC-Onco risk score[63]	Colorectal, oesophago-gastric, lung, or pancreatic, n=391	GRSBMI >25 VTE Family history Primary tumor site Tumor stage	6-month analysis: AUC=0.73 (internal validation)	-
Thrombo-Nsclc risk score[72]	NSCLC patients, n=90	High FVIII High sP-selectin	AUC = 0.93	-
A novel nomogram-based risk assessment model[73]	Lung cancer Derivation cohort, n=819 Validation cohort, n=351	Overweight (BMI 24-28) Adenocarcinoma histology Stage III-IV disease Central venous catheter (CVC) D-dimer ≥2.06 mg/L Prothrombin time (PT) ≥11.45 s Fibrinogen (Fbg) ≥3.33 g/L Triglycerides (TG) ≥1.37 mmol/LROS1 rearrangement History of chemotherapy History of radiotherapy	Derivation cohort, AUC 0.865,95% CI: 0.832-0.897 Validation cohort, AUC 0.904,95% CI: 0.869-0.939	-
Systemic Immune-Inflammation Index and Prognosis Nutritional Index for the Diagnosis of Venous Thromboembolism in Gastrointestinal Cancers[64]	Esophageal cancer, gastric cancer, colorectal cancer, pancreatic cancer, hepatobiliary malignancies Training cohort, n=1326 External validation cohort, n=250	PNI prognosis nutritional index SII systemic immune-inflammation index Age Tumor location Therapy D-dimer	Training cohort, 0.832 (95% CI 0.810~0.855) External validation cohort, 0.822 (95% CI 0.764~0.881)	-
Lung-HYPERCAN VTE risk score[74]	NSCLC, n=568	ECOG performance, D-dimer	6-month VTE incidence: Low-risk: 6% High-risk: 25%	-
Validation of venous thromboembolism predictive model in hematologic malignancies[75]	Hematologic malignancies Derivation cohort, n=285 Validation cohort, n=211	Hypercholesterolemia, tumoral activity, use of t hrombogenic drugs, diabetes mellitus, immobilization	6-month VTE incidence: Derivation cohort, 81.7% positive predictive value Validation cohort, positive predictive value 67.7%	-
DNA Liquid Biopsy Predicts Cancer-Associated TE[7]	NSCLC, breast, pancreatic, melanoma, prostate, bladder, GI, others Derivation cohort, n=4141 Validation cohort, n=1426 Generalizability cohorts, n=463	+ctDNA, Khorana score, No organ sitecf DNA, Chemotherapy	6-month VTE incidence: Derivation cohort, C-index 0.75 Validation cohort, C-index 0.73 Generalizability cohorts, C-index 0.67	-

formation, without the need for additional laboratory testing.[57,58] However, its performance varies markedly across different cancer types. For example, in patients with lung cancer, the Khorana score fails to effectively distinguish between different levels of VTE risk.[59] To improve predictive performance, several models have attempted to incorporate additional clinical or laboratory variables. For example, the expanded Vienna CATS model adds D-dimer and soluble P-selectin to the Khorana score, increasing the 6-month cumulative incidence of VTE in the high-risk subgroup to 35%. However, external validation revealed a modest AUC of only 0.57 (95% CI, 0.48-0.66), and the requirement for additional laboratory testing increases cost and operational complexity, limiting its clinical applicability.[57] The CONKO score was specifically developed for patients with pancreatic cancer by excluding body mass index and replacing it with WHO performance status. However, even in the high risk subgroup, the incidence of VTE remained only approximately 10%.[60] For common solid tumors with relatively low baseline VTE risk, such as breast, colorectal, and prostate cancers, the COMPASS-CAT model attempted to improve discrimination by incorporating a broader range of clinical risk factors. Although it performed well in the derivation cohort (AUC=0.85), external validation in a cohort of 3,814 patients showed a substantial decline in performance (AUC=0.62), suggesting potential overfitting and underscoring the impact of cancer heterogeneity on model stability.[61] Similar limitations have been observed with the ONKOTEV score.[58,62] More recently, models incorporating genetic factors, such as TiC-Onco, have shown promise, with approximately 37% of high risk patients developing VTE.[63] Nonetheless, the cost and limited accessibility of genetic testing remain significant barriers to routine clinical implementation. In addition, inflammation and nutrition related parameters, such as the systemic immune-inflammation index (SII) and prognostic nutritional index (PNI), have demonstrated relatively high AUC values in gastrointestinal cancers,[64] but these findings are largely based on retrospective studies and require prospective validation. In a large multinational prospective cohort study, the Khorana, Vienna CATS, PROTECHT, and CONKO risk scores for CAT were systematically validated.[56] The results showed that these models classified approximately 13-34% of patients as being at high risk of VTE, whereas the overall incidence of VTE was only 6.1%. Even among patients categorized as high risk, only 6.5-9.6% ultimately developed VTE. Moreover, the C-statistics ranged from 0.50 to 0.57. Attempts to improve performance by adding laboratory markers, genetic factors, or broader clinical variables have increased complexity and cost without achieving robust external validation. Overall, current models struggle with cancer heterogeneity and lack sufficient positive predictive value, limiting their clinical utility.[56]

Exploring clinical risk models in CAT using thrombin generation assay in endothelialized microfluidic systems

In addition to traditional clinical risk scoring, microfluidic models have emerged in recent years as functional tools to explore the risk of CAT in cancer patients.[76] In this context, we established a OrganoPlate 2-lane artificial vessel system, to functionally evaluate the procoagulant effects of patient plasma on endothelial cells. Collagen based extracellular matrix was first introduced, followed by seeding HUVECs to form an artificial vessel. Plasma samples from patients with esophageal cancer, colorectal cancer, and pancreatic cancer were then perfused through the artificial vessels for 4 h. This allows endothelial cells to be fully exposed to a procoagulant environment derived from the plasma of cancer patients. After removal of patient plasma, NPP was perfused into the system to perform thrombin generation assay, thereby assessing the procoagulant activity of endothelial cells following plasma pretreatment. Thrombin generation within the artificial vessels was continuously monitored using a fluorogenic substrate, enabling quantitative analysis of thrombin generation, and ETP. Using this microfluidic model, we observed no significant differences in plasma pretreatment of endothelial cells in the case of pancreatic and colorectal cancer; thrombin peak and ETP did not differ significantly between patients who did or did not develop VTE during follow-up. In contrast, plasma from esophageal cancer patients who developed VTE significantly enhanced the procoagulant phenotype of endothelial cells, while plasma from patients who did not develop VTE did not exhibit this enhancement.[77] These findings indicate that cancer-associated hypercoagulable states exhibit significant tumor-type-specific heterogeneity, and traditional coagulation assays may fail to capture endothelial-dependent procoagulant alterations. By generating a three-dimensional, endothelialized microvascular chip under continuous flow, this model more faithfully recapitulates *in vivo* vascular and plasma interactions and provides a novel experimental platform for CAT risk assessment.

Future directions and perspectives

During thrombus formation, activation of the coagulation cascade promotes fibrin formation, a major component of venous thrombi.[78] In this process, thrombin plays a central role by amplifying the coagulation cascade, converting fibrinogen to fibrin, and promoting fibrin network formation.[79] Meanwhile, thrombin can also bind to thrombomodulin (TM) on the endothelial surface, thereby exerting anticoagulant effects.[80] Given the central role of thrombin, this study discusses the development of endothelial cell-based microfluidic CAT-on-chip platforms incorporating thrombin generation, and highlights their applications in mechanistic studies and clinical risk prediction of cancer-associated thrombosis. The system enables real-time monitoring of dynamic changes in thrombin levels and thrombus formation within an artificial vessel under controlled flow conditions. Importantly, the commercial microfluidic platform we selected supports parallel analysis of 64 or 96 chips, enabling high-throughput, standardized testing across multiple patient samples or experimental conditions. By integrating endothelialized microvessels, tumor spheroids, and coagulation readouts within a single chip, this platform may facilitate the development of tumor-specific predictive tools and enable more precise stratification of VTE risk in patients with cancer.

Despite recent advances, current microfluidic models for CAT still have several important limitations. A central challenge is that cancer-associated thrombosis is mechanistically heterogeneous, with different cancer types driving distinct dominant thrombotic pathways. Currently, the most widely investigated microfluidic models of cancer-associated thrombosis focus on platelet activation and adhesion.[76,81-84] This is particularly relevant for tumor

types in which platelet-driven thrombosis is prominent, including ovarian cancer, gliomas, lung cancer and stomach cancer.[85-87] Of note, in lung and colorectal cancers, the contribution of leukocyte-related mechanisms to thrombus formation is also not negligible.[86] In an endothelialized microfluidic model, Beckman et al. quantified leukocyte rolling velocity and showed that JAK-STAT inhibition modulates endothelial prothrombotic activation and leukocyte adhesion in myeloproliferative neoplasms (MPNs),[88] providing a framework that could be extended to model leukocyte-driven thrombosis in lung and colorectal cancer. Meanwhile, accumulating evidence indicates that NET formation also exerts a pronounced prothrombotic effect and have been reported across multiple malignancies, including pancreatic cancer, lung cancer, and hepatocellular carcinoma.[89,90] However, microfluidic chip platforms designed to model thrombosis mediated by immune cells remain at an early stage of development. For example, these platforms have limited capacity to fully recapitulate the initiation and amplification of thrombosis driven by immune cell involvement, particularly the dynamic effects of NETs, monocyte derived tissue factor, and platelet-leukocyte interactions observed in vivo. Furthermore, the relationship between thrombin generation parameters from chip systems and clinically defined hypercoagulable states is not yet fully understood, which currently limits their use as independent clinical risk prediction tools.

Moreover, in many current microfluidic models, HUVECs remain the predominant endothelial cell type used to construct endothelialized artificial vessels. Because HUVECs are a stable, readily accessible, and easy-to-culture endothelial source, they are widely used in CAT-on-chip studies. However, endothelial cells exhibit marked heterogeneity across vascular beds and disease microenvironments, with arterial, venous, and cancer-associated endothelium differing in both molecular expression profiles and functional phenotypes.[91] Therefore, HUVECs may not fully recapitulate the key molecular features and functional responses of tumor-associated or peripheral venous endothelium that directly contribute to CAT pathogenesis.[92] The incorporation of patient-derived cellular components into microfluidic systems may enable more faithful reconstruction of the CAT microenvironment. Specifically, individualized vascular endothelium can be generated using patient-derived endothelial sources, including endothelial colony-forming cells (ECFCs), iPSC-derived endothelial cells, or primary endothelial cells obtained from disease-relevant vascular beds (e.g., pulmonary artery endothelial cells from patients with chronic thromboembolic pulmonary hypertension, CTEPH).[93-96] In parallel, patient-derived tumor cells, tumor tissues, or tumor-secreted factors can be integrated into chip platforms to model tumor-vascular-coagulation interactions *in vitro*.

In addition, perfusion of whole blood through microfluidic chips is critical for realistically modeling CAT. Compared with plasma systems, whole blood preserves leukocyte and platelet populations that are activated or remodeled under tumor influence, thereby enabling a more accurate representation of the interplay between the immune and coagulation systems. This is particularly important for studying leukocyte recruitment, platelet-leukocyte aggregate formation, and immune-driven amplification of coagulation responses.

Moreover, functional coagulation phenotypes measured by microfluidic platforms (such as thrombin generation, changes in endothelial permeability, and inflammatory responses) can be systematically correlated with longitudinal clinical outcomes. Such integrated analyses can help establish the novel functional biomarkers, supporting individualized risk stratification and providing direction for prophylactic anticoagulation. In conclusion, with the increasing integration of patient-derived samples, multicellular components, and multi-parameter dynamic measurements, microfluidic platforms hold promise for connecting mechanistic studies and clinical risk prediction in CAT, offering a new solution to overcome the limited predictive performance of existing clinical models.

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