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Review Article

Cancer-associated thrombosis in cholangiocarcinoma: Exploring a phenotype of tumor aggressiveness

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ABSTRACT

Cholangiocarcinoma (CCA) is the liver malignancy with the most rapid increase in incidence and lethality in recent years. Venous thromboembolism (VTE) is a common complication of the cancer-associated hypercoagulable state, which may incite tumor progression and dissemination, thereby increasing cancer-related morbidity and mortality. Compared to other cancer types, occurrence of VTE in CCA has been underestimated, though recent evidence indicates it may behave as prognostic factor of worst outcome. Given the need for novel predictive scores and treatment approaches when VTE occurs, identifying subgroups of patients with CCA who would benefit from thromboprophylaxis without increasing the risk of bleeding is a crucial but still neglected aspect of the management. The aim of this review is to summarize current observations on the clinical significance, prediction, risk assessment and the underlying mechanisms of cancer-induced thrombogenesis in CCA, as well as to identify research areas ripe for prioritization in the near future.

1. Introduction

Cholangiocarcinoma (CCA) is a rare primary liver malignancy, with features of biliary differentiation, which may originate from cholangiocytes as well as from hepatocytes and liver progenitor cells [1]. CCA encompasses several distinct anatomic subtypes, including intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA), which are characterized by differences in etiology, risk factors, clinical presentation, therapeutic strategies, and prognosis. Worldwide, new diagnoses range between 0.3 and 6/100,000, resulting in 1–6/100,000 deaths per year [1]. Currently, several studies indicate that CCA incidence, particularly iCCA, is increasing worldwide, making this disease a growing health problem [1,2]. Unfortunately, early detection of CCA remains a major challenge because of the absence of early warning signs and reliable biomarkers, which means that therapeutic options are very limited when the tumor stage is advanced [3].

Increasing evidence suggests that coagulation abnormalities are closely related to tumor growth, progression, metastasis, and prognosis.

Abbreviations: 5-FU, 5-fluorouracil; ADP, adenosine diphosphate; AT, antithrombin; CAF, cancer-associated fibroblasts; CAT, cancer-associated thrombosis; CA-19-9, Carbohydrate antigen 19–9; sialyl, Lewis serum antigen; CCA, cholangiocarcinoma; CP, cancer procoagulant factor; CRC, colorectal cancer; CRP, C-reactive protein; dCCA, distal cholangiocarcinoma; DOACs, direct oral anticoagulants; DVT, deep vein thrombosis; EMT, epithelial-mesenchymal transition; EVs, extracellular vesicles; GBC, gallbladder cholangiocarcinoma; GI, gastrointestinal cancer; HCC, hepatocellular carcinoma; HNSCC, neck squamous cell carcinoma; iCCA, intrahepatic cholangiocarcinoma; IL, interleukin; KRS, Khorana Risk Score; LMWH, low molecular weight heparin; MMPs, metalloproteinases; MUC, mucins; NETs, neutrophil extracellular traps; NSCLC, non-small cell lung cancer; pCCA, perihilar cholangiocarcinoma; PDAC, pancreatic ductal adenocarcinoma; PDGF, platelet-derived growth factor; PDPN, podoplanin; PVT, portal vein thrombosis; PE, pulmonary embolism; RAMs, risk assessment models; SVT, splanchnic vein thrombosis; TAM, tumor-associated macrophage; TAN, tumor-infiltrating neutrophils; TF, tissue factor; TME, tumor microenvironment; TNF, tumor necrosis factor; TXA2, thromboxane A2; VEGF, vascular endothelial growth factor; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor; VTE, venous thromboembolism.

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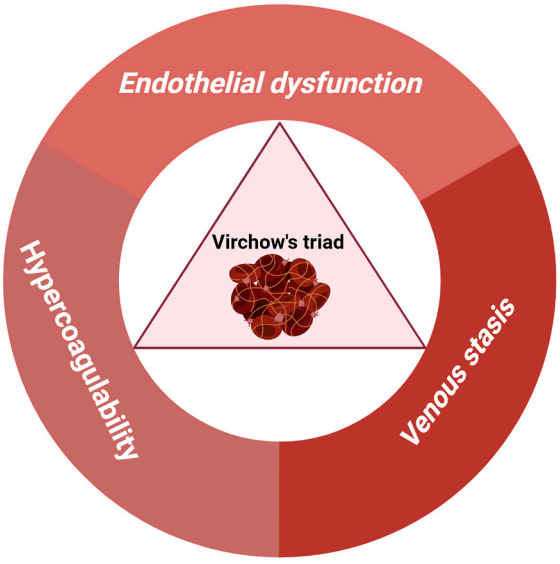
Indeed, thromboembolic disorders have been frequently described in patients with different types of cancer [4,5]. The mechanisms of cancer-associated thrombosis (CAT) are complex and multifactorial, but overall, are sustained by the generation of an intrinsic hypercoagulable state, which may lead to venous thromboembolism (VTE) as the most feared manifestation. The occurrence of VTE in cancer has devastating effects, as it is associated with increased need for hospitalization, possible delay or suspension of systemic cancer therapy, significant rise in costs associated with cancer treatments, and higher mortality [4]. Although VTE is a known risk in patients with liver tumors, especially hepatocellular carcinoma (HCC) [6], diagnosis of VTE in the context of CCA is often overlooked and the underpinning mechanisms remain obscure. Thus, adoption of prophylactic measures might be key in the clinical management of this pathology. In this perspective, the present review aims to summarize the most recent observations regarding the clinical assessment of VTE risk and underpinning mechanisms in CCA patients. Since published data on this research field are relatively scarce, in this manuscript some assumptions on CAT pathogenesis in CCA have been inferred from studies performed in other types of solid tumors, when the related concepts may apply to CCA biology.

2. Clinical significance of cancer-associated VTE

Cancer-associated VTE was described for the first time by the French physician Armand Trousseau (1801–1867) in 1865 [7], paving the way for a wide range of studies identifying thrombosis as a serious complication in cancer patients. VTE, which encompasses pulmonary embolism (PE) and deep vein thrombosis (DVT), significantly contributes to the morbidity and mortality of patients with cancer and is considered the second leading cause of death related to cancer progression [8,9].

Although DVT and PE remain the most frequent and well-characterized manifestations, several less common but clinically relevant forms of VTE have been increasingly identified in cancer patients [10]. These include: i) superficial vein thrombosis, traditionally perceived as a benign condition, but increasingly recognized as a marker of systemic hypercoagulability in malignancy [11]; ii) splanchnic vein thrombosis (SVT), including portal vein thrombosis (PVT), which is frequently observed in gastrointestinal (GI) and hepatocellular cancers [12]; iii) cerebral venous sinus thrombosis, which has been reported in patients with solid tumors (cerebral or non-cerebral) as well as with hematologic malignancies [13]. Additionally, vena cava thrombosis,



Endothelial dysfunction

- Direct tumor vascular invasion
- Pro-inflammatory cytokines released in the tumor microenvironment (e.g. IL-1β , IL-6, IL-8, TNF-α)
- Platelet mediators released in the tumor microenvironment (e.g. ADP, TXA_2, PF4, P-selectin)
- Central venous catheter placement
- Biliary stent placement
- Chemotherapy: platinum-based agents, dasatinib, VEGFR-TKI
- Radiotherapy

Venous stasis

- Immobility or prolonged bed rest after surgery
- Compression of blood vessels by tumor cell infiltrates (vascular encasement)

Hypercoagulability

- Pro-inflammatory cytokines released in the tumor microenvironment (e.g. IL-1β , IL-8, TNF-α, VEGF)
- Platelet mediators released in the tumor microenvironment (e.g. PF4, fibrinogen, PAF, P-selectin, EVs)
- Procoagulant mediators released in the tumor microenvironment (e.g. FVII, FX, TF, vWF)
- Major surgery: hepatic resection, liver transplant
- Biliary drainage
- Chemotherapy: platinum-based agents

Fig. 1. Virchow's triad [19] in patients with cholangiocarcinoma (CCA) (created in BioRender.com). In cholangiocarcinoma (CCA), all three components of Virchow's triad (endothelial injury, blood flow stasis, and hypercoagulable state) are frequently involved because of cancer-related local and systemic processes. These pathological alterations act synergistically to substantially increase the risk of venous thromboembolism (VTE) in affected patients. Endothelial injury may result from direct tumor invasion, or treatment procedures, including device placement and therapeutic approaches, i.e. chemotherapy and radiotherapy. Simultaneously, blood flow stasis can occur due to prolonged immobility, or local tumor-associated vascular compression. The hypercoagulable state is often exacerbated by the release of a wide array of prothrombotic mediators from tumor cells, the surrounding stromal and immune cells, and platelets, which may also induce endothelial injury. The list of molecules potentially shaping a prothrombotic milieu is huge and include procoagulant factors as well as proinflammatory mediators, collectively driving the thrombo-inflammatory processes featuring CCA. In addition, treatment procedures performed in CCA (surgical resection, liver transplantation, biliary drainage, platinum-based therapies, TKIs), may stimulate further procoagulant mechanisms.

involving either the superior or inferior vena cava, may result from direct tumor invasion or external compression, particularly in lung or renal cancers [14,15]. Post-thrombotic syndrome, a common chronic complication following DVT [16], and paradoxical embolism, often related to intracardiac or intrapulmonary shunts [17], have been reported in the context of cancer-associated VTE [10,18]. All of these thrombotic manifestations highlight the wide and multifaceted landscape of thrombotic events in malignancy, emphasizing the need for vigilant evaluation and personalized management strategies.

VTE commonly develops in areas of reduced circulation, such as venous valves, where accumulation of fibrin deposits activates clotting factors, promoting thrombus formation. This process occurs in the presence of one or more components of Virchow's triad - vascular endothelial injury, venous stasis, and hypercoagulability -, as illustrated in Fig. 1 [19,20].

Until recently, the incidence and temporal evolution of VTE complications in cancer patients were poorly understood, but currently, multiple studies have shown a persistent increase in incidence of cancer-associated VTE, reaching a 3-fold increase in the 12-month cumulative incidence over the last decade [21,22]. The incidence of thrombotic events in cancer patients has been unevenly reported across different types of primary solid tumors, with the highest risk reported in patients with pancreatic, brain, lung, GI, and ovarian cancer [23–25].

The pathogenesis of VTE in cancer patients involves a complex and dynamic interplay between tumor cells and various elements of the host response to cancer, particularly those involved in the hemostatic system [10,26,27]. Tumor cells can trigger the coagulation cascade through multiple mechanisms, which include the release of pro-inflammatory and pro-angiogenic mediators, as well as fibrinolytic and procoagulant factors, in concert with the varied secretory functions of the stromal cells recruited in the tumor microenvironment (TME). In addition, expression of a multitude of adhesion molecules by endothelial cells may mediate interaction with blood cells [25].

Recent evidence has pinpointed that patients with CCA also harbor a hypercoagulable state and present several tumor- and host-related factors that may affect all three components of Virchow's triad (Fig. 1).

3. Incidence of VTE in CCA

Incidence of VTE in the cancer population varies widely depending on the tumor type, cancer stage, anticancer therapy, and comorbidities [28–30]. Irrespective of cancer type, the risk of VTE within the first six months following a cancer diagnosis is approximately 12 times higher than in the general population, and increases to 23 times higher in patients undergoing chemotherapy [21,31]. In addition, patients with hematological, lung and GI malignancies with a prior episode of VTE have a 6- to 7-fold increased risk of VTE recurrence when compared to patients without a history of VTE [32]. The incidence of cancer-associated VTE has increased over the last decades. According to a population-based cohort study, the incidence trend of VTE in patients with solid and hematological malignancies increased from 1.0 % in 1997 to 3.4 % in 2017 [21]. Notably, the highest VTE rates within the first six months after cancer diagnosis were observed in patients with GI cancers, including esophageal, pancreatic, gastric, hepatic, and colorectal tumors [21]. As summarized in Table 1, despite substantial variability across the different primary sites, the overall the rate of VTE in patients with GI cancer is much higher than non-GI cancers (8.6 vs 3.3 %) [33].

Table 1
Incidence of venous thromboembolism in gastrointestinal tract cancer.

Cancer type	Incidence rate/1000 persons per year	References
Pancreatic	98–133	[21,29,30]
Biliary	71	[21]
Colorectal	36–84	[21,30]
Liver	35–82	[21,29,30]
Esophagus	13–52	[21,29,30]
Stomach	36–37	[29,30]

In CCA, development of VTE has gained increasing interest thanks to recent studies performed in miscellaneous population cohorts, including different subtypes of CCA, with and without surgical procedures [5]. A study performed in 273 patients with CCA reported an incidence of VTE of 14.65 %, with 14 patients developing pulmonary thromboembolism with or without DVT, 18 presenting PVT, 4 with inferior vena cava thrombosis, and 4 with hepatic vein thrombosis [34].

In a retrospective study of 133 CCA patients, VTE events were documented in 29.3 %, arterial thrombosis in 19 % and PVT in 33 % of the cases [5]. More recently, in a cohort of 332 advanced-stage CCA patients, 35.5 % developed VTE, with 38.5 % of cases identified at diagnosis, and 22.4 % and 32.8 % occurring at 3 and 12 months, respectively. PVT emerged as the most frequent VTE manifestation. Importantly, VTE occurrence was associated with significantly reduced survival, highlighting its prognostic relevance [35].

Surgical procedures further increased the risk of VTE in CCA patients. A fatal PE complicating Trousseau's syndrome was reported in a case of CCA who underwent liver biopsy [36]. In a retrospective study of 27 patients with iCCA and pCCA undergoing hepatic resection, VTE occurred in 6 patients (22 %), including 2 cases of DVT (on days 7 and 45 postoperatively) and 4 cases of PVT, both in the immediate postoperative period (within 24 h) and in the long-term (40–60 days after surgery) [37]. Similarly, in a cohort of only iCCA, surgically resected patients developed PVT in 19.4 % [38], while a pro-coagulant state was found in 22.6 % iCCA patients after curative resection [39]. Likewise, VTE incidence reached 36.2 % in dCCA patients after surgery [40]. Importantly, the median survival time of iCCA with PVT was 12.68 months, compared to 28.91 months of iCCA without PVT, indicating the prognostic significance of VTE even in the context of CCA [38].

CCA patients are also at risk for SVT, a rare manifestation of VTE occurring in the splenic, mesenteric, portal, and hepatic veins circulation (Budd-Chiari syndrome) [41], either at the time of diagnosis [42] or after surgical resection [43]. Interestingly, the risk of recurrent thrombosis in cancer-associated SVT was similar to that of cancer-associated VTE in usual sites [44]. Indeed, SVT was reported in 27 out of 40 CCA patients who experienced VTE [34]. Taken together, these data support the need for a comprehensive thrombotic risk assessment in CCA patients, including unusual thrombotic sites such as the splanchnic venous system, which may be particularly relevant if surgical intervention is considered.

4. Risk factors and assessment models for CCA-associated thrombosis

In cancer patients, VTE represents a feared complication that may occur at any time during the disease, in relation to a range of risk factors, including patient comorbidities, type of cancer, history of prior VTE, and surgical and chemotherapeutic treatments, among others [45]. Risk factors for VTE deserve careful consideration in the diagnostic work-up of CCA as well [40,46], since surgical resection, radiotherapy, chemotherapy, and eventually, immunotherapy, and targeted therapy, offered to these patients, may further increase this risk [47,48]. Other risk factors, commonly present in CCA, such as advanced age and reduced performance status, which constrain the patient to prolonged immobility, must be considered [26,49].

In addition to surgery, chemotherapy protocols are another important risk factor for VTE in CCA patients. The incidence of VTE associated with chemotherapy ranges from 10 % to 20 % depending on the type of drug administered [26]. Notably, cisplatin-based therapies, including the combination of cisplatin with gemcitabine, the standard of care for advanced CCA [50], are associated with a high number of thromboembolic events (169/932 patients) [51]. Moreover, 5-fluorouracil (5-FU), in combination with other chemotherapeutics (FOLFOX), a second-

line regimen recently proposed for patients with CCA, also harbors a consistent risk of VTE, ranging from 15 to 17 % [26,47]. Indeed, the highest risk of VTE in CCA is reported in patients undergoing surgery and chemotherapy (Table 2). However, in CCA patients, a validated algorithm for VTE risk stratification and management is lacking.

Risk assessment models (RAMs) are defined as a combination of multiple predictors by which the risk of a specific endpoint in individual patients can be calculated, and for VTE, they provide a guide to determine the need of thromboprophylaxis strategies. In solid organ tumors, the currently available RAMs are the Khorana Risk Score (KRS), the new Vienna-CATS score, the MD Anderson Cancer Center (MDACC)-CAT model, the COMPASS-CAT score, and the new generation of KRS-based scores [52] (Table 3). By evaluating readouts of cancer thrombogenicity, they offer the possibility to tailor the risk of CAT for each patient in the specific cancer setting. These models combine clinical factors such as cancer progression, chemotherapy treatments, comorbidities, and specific hypercoagulability biomarkers to identify high-risk patients for VTE [53]. Some models incorporate cancer type directly by assigning specific points based on tumor type (e.g., KRS, COMPASS-CAT, PROTECHT, CONKO, and TiC-Onco), reflecting the heterogeneous thrombotic potential across malignancies. In contrast, other models, such as ONKOTEV, New Vienna-CATS, MDACC-CAT, and CATS, do not explicitly include cancer type as a scoring variable; however, their risk predictions may still be indirectly influenced by tumor biology through clinical parameters (e.g., metastases) or related laboratory markers (e.g., elevated D-dimer, P-selectin) [52,53].

Most of these predictive models have been developed from retrospective studies of cancer outpatient's cohorts. Thus, substantial variability exists among RAMs, with strengths and weaknesses depending on the type of cancer and the statistical approach taken [52]. Unfortunately, CCA is not consistently represented in all these scores, as it remains a relatively understudied malignancy. Consequently, the relative risk for VTE in CCA has not clearly established, notwithstanding that it appears to be comparable to other tumors more classically recognized as thrombogenic, either before or after diagnosis [5,54]. This consideration is supported by a multivariate analysis study within the existing RAMs, which confirmed CCA as a high-risk tumor for VTE and showed ONKOTEV score as the only reliable predictor of VTE events in CCA patients. Interestingly, elevated serum levels of carbohydrate antigen 19–9 (CA19–9, sialyl Lewis serum antigen), a tumor biomarker associated with stage and prognosis of CCA [50,55], and of C-reactive protein (CRP), an index of ongoing inflammatory response likely associated with cancer activity [56], behaved as independent risk factors for thrombosis [5]. In another prospective study, the widely used risk scores KRS, Vienna-CATS score, PROTECHT, ONKOTEV, and CATS Score evaluated the risk of VTE in patients with different types of cancer. Notably, the highest rate of VTE was observed in CCA patients (60 %), much more than breast (30 %), gynecological (14 %), gastric (14 %) and colorectal (14 %) cancer [54]. Among diverse blood biomarkers, including immature platelet fraction (IPF), mean platelet volume (MPV), P-selectin, and D-dimer, only D-dimer predicted the VTE risk [54]. However, whether CAT affects the CCA patient outcome is currently unknown, and thus, the refinement of existing RAMs may help to better assess the prognosis of these patients.

5. Potential mechanisms underlying CCA-associated thrombosis

Thrombotic events in cancer patients are driven by pathophysiological mechanisms that are distinct from those underlying thrombosis in non-cancer populations. Pathways associated with tumor cell proliferation may also drive the production of various mediators that trigger a hypercoagulable state in cancer patients [69]. The release into the bloodstream of tissue factor (TF), TF-positive tumor-derived extracellular vesicles (EVs), podoplanin (PDPN), cancer procoagulant factor (CPF), neutrophil extracellular traps (NETs), heparinase, and other inflammatory molecules, may potently activate the blood-clotting cascade, leading to thrombosis [70,71]. In addition, depending on the tumor type, other pathways, unleashed by the production by cancer cells of thromboxane A2 (TXA2) and platelet agonist adenosine diphosphate (ADP), as well as by cathepsin cysteine proteases and matrix metalloproteinases (MMPs), may also activate platelets, leading to thrombus formation [9,72,73].

The underlying mechanisms of CAT in CCA have been significantly less investigated compared to HCC, the most common primary liver cancer, or pancreatic ductal adenocarcinoma (PDAC), which shares similar desmoplastic and biological features with CCA [5,6,27]. Conceivably, patients with CCA may develop a hypercoagulable state, elicited by the tumor itself or by the surrounding stromal reaction, whereby platelet mediators are actively produced [74]. As a result, either a multitude of procoagulant factors are released within the TME or various processes that promote coagulation at the endothelial level are unleashed (Fig. 2). The putative factors governing these mechanisms are herein discussed.

5.1. Tissue Factor (TF)

TF, also known as coagulation factor (F) III, is the initiator of the coagulation cascade through the formation of the TF-FVII/VIIa complex, followed by the activation of FX, which cleaves prothrombin to thrombin, to induce thrombus formation (Fig. 2). Several observations indicate that TF expression is upregulated in several tumor cell types [32,49,75], due to the inactivation of tumor suppressor genes, such as *TP53* and *PTEN* [76] and/or by the activation of oncogenes, including *MET* and *KRAS* [77], which mutations or alterations are frequent in CCA [78]. Furthermore, tumor necrosis factor (TNF)-α and interleukin (IL)-1β, both secreted by tumor cells, upregulate TF levels in endothelial cells lining the blood vessels of the TME [79,80]. In addition, TF blood levels are increased in patients with cancer, harbored by EVs secreted by neoplastic and immune cells [75].

TF overexpression has been reported in several cancer tissues, including glioblastoma, PDAC, head and neck squamous cell carcinoma (HNSCC), esophageal, bladder, breast, non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and gastric, cervical, ovarian, endometrial, and prostate cancers [81]. Although increased expression of TF across different subtypes of CCA was sporadically observed [82], evaluation of a panel of TF pathway-related coagulation biomarkers in 41 patients with CCA reported levels of FVIIa-Antithrombin (AT), FVII antigen (FVII Ag), total and free TF pathway inhibitor (TFPI) and TF-EVs-procoagulant activity to be higher than in HCC and CRC patients. Interestingly, high levels of FVIIa-AT plasma levels were associated with

Table 2
Specific risk factors for thrombosis in Cholangiocarcinoma.

Risk factor	VTE risk	References
Surgery	22 % of cases with CCA had a thrombotic event after liver resection.	[37]
	High prevalence of VTE (36.2 %) in patients undergoing dCCA surgery (177 patients). Median overall survival of 31 months vs. 67 months without VTE.	[40]
	8 % of cases with PVT in the first post-operative week after hepatectomy for pCCA (86 patients).	[46]
	Recurrent acute VTE in pCCA patients after hemihepatectomy (a case report).	[57]
Chemotherapy/ Vein catheter	Chemotherapy treatment was related to the occurrence of VTE in CCA patients.	[34]
	PICC was associated with DVT in a patient with metastatic CCA undergoing chemotherapy.	[58]

Table 3
Risk assessment models in solid organ tumors.

Risk assessment models (RAMs)		Risk Score (RS)	Cancer type points		Hematological markers	Other considerations	References
KRS		0: Low risk 1–2: Intermediate risk ≥3: High risk	Stomach Pancreas Lung Bladder Renal Ovarian Testicular Lymphoma	2 2 1 1 1 1 1 1	Prechemotherapy, levels of hemoglobin, platelets and white blood cells,	Body mass index (BMI), erythropoietic stimulating agents	[59,60]
New Vienna-CATS score		0: Low risk 1–2: Intermediate risk ≥3: High risk	Pancreas Stomach Lung Bladder Esophagus Breast Colorectal Urothelial Kidney Ovarian Uterine Cervical Lymphoma Pancreas Gastrointestinal (non-pancreas) Head/neck	Based on biomarkers and individual clinical history. E.g. P-selectin >53.1 ng/mL- 1 D-dimer >1.44 μg/mL-1 history of VTE- 1	D-dimer and P- selectin levels	Tumor histology, clinical history of VTE	[60,61]
MDACC-CAT model		Nomogram scaling	Lung Breast Genitourinary (non-kidney) Kidney Gynecological Lymphoma	–	Hemoglobin analysis, white blood cell and platelet count	Tumor histology, metastasis, use of platinum-based chemotherapy and erythropoietin-stimulating agents	[62]
COMPASS-CAT		≤6: Low/ intermediate >7: High risk	Lung Colorectal Ovarian Breast	2 2 2 0	Platelet count	Time of cancer diagnosis, stage of cancer, personal history of VTE, presence of cardiovascular risk, hospitalization for acute medical illness, central venous catheter, use of anthracycline or antihormonal therapy	[63]
KRS-based scores	CATS Score	Nomogram scaling	Stomach Pancreas Lung Bladder Gynecological Testicular lymphoma	–	Hemoglobin, platelet and white blood cell count, D-dimer and soluble P-selectin levels	NA	[52]
	PROTECHT Score	0: Low risk 1–2: Intermediate risk ≥3: High risk	Pancreatic Gastrointestinal Lung Ovarian	Idem KRS + 1 point for gemcitabine or platinum-based chemotherapy	Hemoglobin, platelet and white blood cell count, D-dimer and soluble P-selectin levels, Thrombin generation	Use of gemcitabine, cisplatin, or carboplatin therapy	[64,65]

(*continued on next page*)

Table 3 (*continued*)

Risk assessment models (RAMs)	Risk Score (RS)	Cancer type points		Hematological markers	Other considerations	References
		Breast	1			
		Head and neck	1			
	CONKO Score	Pancreatic Cancer	2	Hemoglobin	Use of gemcitabine, fluorouracil, folinic acid, and cisplatin therapy	[66]
	TiC-Onco risk score	Pancreatic or Gastrointestinal	2	Hemoglobin, platelet and white blood cell count	Genetic risk, primary tumor site, tumor node metastasis stage, and body mass index (BMI), history of VTE, the presence of diabetes, hypertension, and high blood cholesterol level	[52,67]
		Lung Gynecological Bladder	2			
		Testicular Lymphoma	1			
			1			
			1			
			1			
		Pancreatic	2			
		Gastrointestinal Lung	1			
		Breast	1			
	ONKOTEV Score	Head and neck Skin	KRS $\geq 2 = 1$	Pre-chemotherapy hemoglobin, platelet and white blood cell count	Metastatic disease, history of VTE, vascular/lymphatic macroscopic compression	[68]
		Brain				
		Kidney Hepatocellular carcinoma Neuroendocrine				
		Genito/urinary tract tumors				

upregulated expression of TF mRNA and increased risk of mortality [83]. Despite this study did not analyze the thrombotic events, FVIIa-AT plasma levels were predictive of CCA patients with high TF values, and thus, they may regulate TF expression (Fig. 2). These findings suggest that thrombogenesis represents a critical pathological event in CCA patients, and in this respect, FVIIa-AT might serve as a useful readout of tumor-associated hypercoagulation (Fig. 3).

5.2. Platelet activation

Platelet activation has been widely recognized as a key step in thrombogenesis in cancer patients. Tumor cells may activate platelets by direct adhesion and/or by secreting a vast array of platelet-activating factors, such as tumor-derived EVs, TF, PDPN, and ADP (Fig. 2) [84,85]. Interestingly, the human iCCA cell line HuCCT-1 has been shown to induce platelet aggregation by activating thrombin generation and stimulating TXA2-induced cyclooxygenase [86]. Platelet hyperactivation has been reported in CCA patients, and interestingly, platelet-derived growth factor (PDGF) promoted invasion and metastasis of CCA tumor cells by increasing MMP2 and MMP9 expression and inducing epithelial-mesenchymal transition (EMT) via the p38/MAPK signaling pathway [87]. Furthermore, a member of the PDGF family, PDGF-D, secreted by tumor cholangiocytes upon hypoxia stimulation, regulates recruitment of cancer-associated fibroblasts (CAF) and provides them with lymphangiogenic capabilities, further supporting the important role of platelet-related soluble factors in shaping the CCA microenvironment [74]. It is tempting to speculate that this mechanism may also cooperate with the generation of an environment conducive to platelet activation.

5.3. Podoplanin (PDPN)

PDPN is a transmembrane glycoprotein that induces platelet activation through interaction with C-type lectin-like receptor 2 (CLEC-2), which is expressed on platelets (Fig. 2). By interacting with CLEC-2, tumor-derived PDPN promotes venous thrombosis by triggering the release of procoagulant factors and other mediators from platelet granules [88,89]. Although the mechanistic link between PDPN secretion and platelet aggregation has not been fully elucidated, increasing evidence suggests that PDPN expression on tumor cells, as well as the release of PDPN-positive EVs, are pivotal players in the development of CAT [90,91]. Interestingly, in CCA patients, PDPN is widely overexpressed by tumor epithelium, tumor reactive stroma (mainly CAFs) and lymphatic endothelium, behaving as a modulator of the TME [92]. Given its involvement in cell growth, inflammation, tumor-associated vascularization, and lymphangiogenesis, and thrombosis [74,88,89], PDPN might act as molecular effector of thrombogenesis promoted by CAFs, and represents a putative predictive biomarker for CCA patients at higher risk of VTE development.

5.4. Pro-inflammatory cytokines

Malignant cholangiocytes produce and release a vast array of pro-inflammatory cytokines (Fig. 2) [93], which can instruct endothelial cells to gain a procoagulant phenotype [94]. Among them, IL-1β, IL-6, IL-8, and TNFα upregulate procoagulant factors while downregulating anticoagulant pathways and inhibiting fibrinolysis [95]. In particular, IL-6 stimulates thrombocytopoiesis by activating megakaryocytes [96], and upregulating thrombopoietin expression by hepatocytes [97]. Similar effects are induced by TNFα, which promotes the overexpression of TF, and inhibits endothelial cell protein C receptor (ECPCR) and thrombomodulin [98]. IL-1β is synthesized by activated platelets and is released within platelet EVs to interact with other inflammatory cells. Furthermore, IL-1β can also induce platelet activation via autocrine mechanisms [99]. Finally, IL-8 expression has been shown to induce NET production and granulocyte chemotaxis [100]. Although the direct

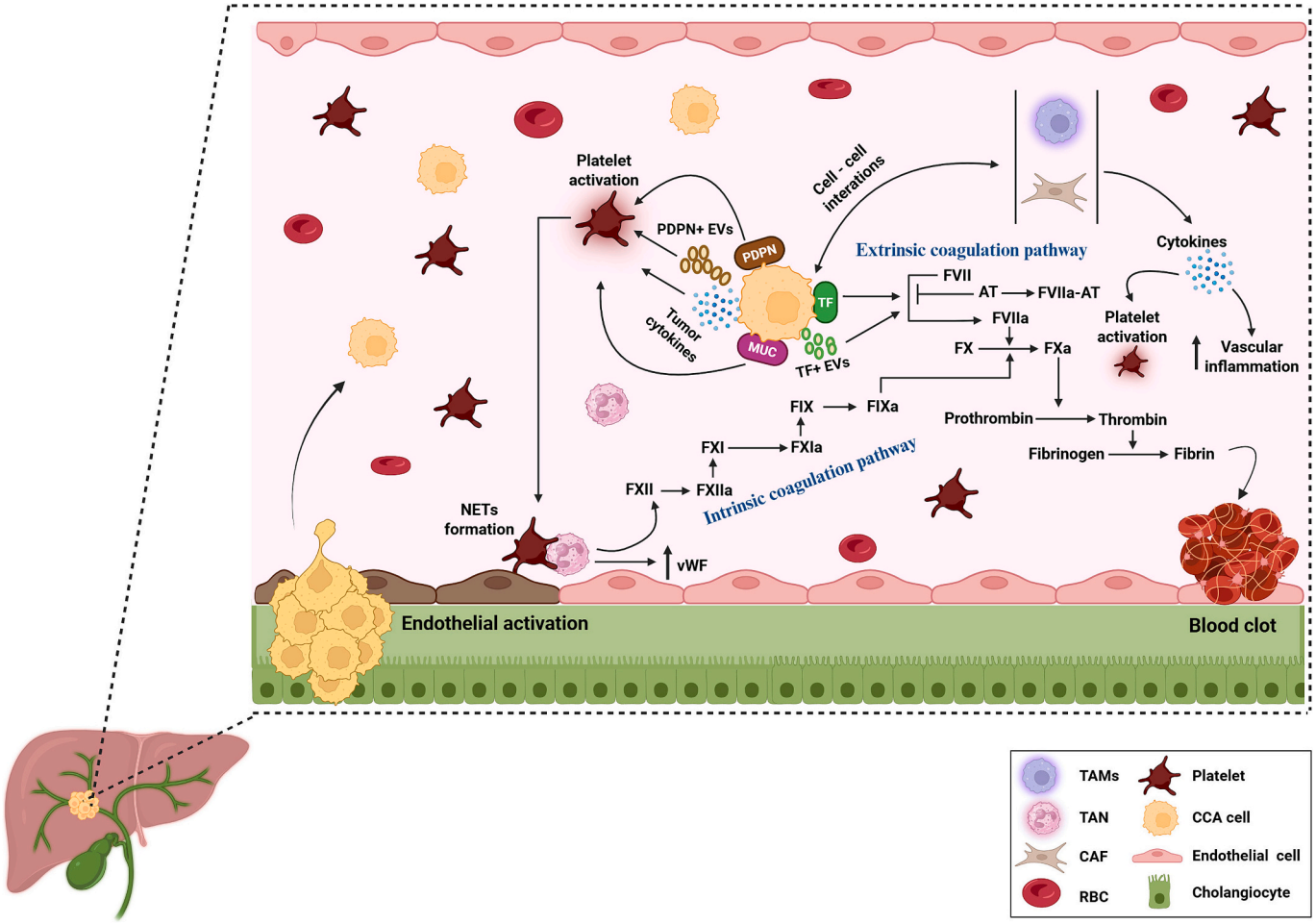


Fig. 2. Putative mechanisms involved in CCA-associated thrombosis (created in BioRender.com). Circulating CCA cells can release TF-positive tumor-derived extracellular vesicles (EVs) and express tissue factor (TF), which binds factor (F) VII/FVIIa to initiate extrinsic coagulation cascade by activating FX/FXa, with consequent thrombin generation and fibrin clot formation. The procoagulant activity driven by this pathway is modulated by antithrombin (AT) through the formation of FVIIa–AT complexes. Tumor cells may also release pro-inflammatory cytokines (IL-1β, IL-6, IL-8, and TNFα), podoplanin (PDPN)-positive tumor-derived extracellular vesicles (EVs) and express mucins (MUC) and PDPN, which induce platelet activation and aggregation. In addition, cell-cell interaction promotes the release of pro-inflammatory cytokines by tumor-associated macrophages (TAMs) and cancer-associated fibroblasts (CAF) inducing vascular inflammation and platelets activation. Furthermore, neutrophil extracellular traps (NETs) generated by tumor-infiltrating neutrophils (TAN), activate endothelial cells with increased von Willebrand factor (vWF) secretion. By providing a scaffold for platelet adhesion, they induce activation of FXII, which initiates the intrinsic coagulation pathway through FXI/FXIa and consequently, FX/FXa activation.

contribution of these cytokines to thrombotic events in CCA has not been elucidated, the increase in IL-6 has been observed in both bile and serum of CCA patients [101] as well as in several CCA cell lines [102]. Moreover, cell elements hosted in the TME, such as tumor-associated macrophages (TAMs), which produce TNFα, IL-6, and IL-8, and CAFs that produce IL-1β [103], can provide further endothelial cells with phenotypic changes proficient to thrombosis [104].

5.5. *Neutrophil Extracellular Traps (NETs)*

NETs are net-like, filamentous structures released by neutrophils composed of DNA filaments, histone, and protein complexes, that constitute a scaffold for the aggregation of platelets and red blood cells, thereby potently activating coagulation pathways [105]. Prothrombotic mechanisms driven by NETs include activation of FXII and increased release of von Willebrand factor (vWF) (Fig. 2) [106]. NET formation has been strongly connected to CAT [107]. Therefore, in recent years, more attention has been drawn on the role of tumor-infiltrating neutrophils (TAN) driving NET formation [108]. It has been reported that as tumor grows, neutrophils are recruited into the TME, and eventually educated to generate NETs, as observed in diverse types of cancer [109], including breast [110], lung [111], and ovarian cancer [112], HCC [113] and CRC [114]. In turn, uncontrolled release of NETs drives the pre-metastatic niche formation, supporting tumor survival, immune response inhibition, chemoresistance [108,115], and vessel occlusion [115]. CCA-associated TAN can also regulate the immune microenvironment and affect the response to therapeutic treatments [103]. Although little is known about the NET-related functions of TAN in CCA, their ability to form NET could be promoted by malignant cells via paracrine circuits mediated by several cytokines and chemokines, which are summarized in Table 4 [103]. Data presented in this table refer to soluble mediators relevant for CCA biology [103,116–118], which involvement in NET formation has been reported for other more typically NET-associated epithelial cancers and diverse inflammatory conditions [119–124,127]. Consistently, recent evidence has demonstrated the presence of NETs in serum samples of pCCA and dCCA patients [125], as well as in histological samples of iCCA [126]. Noteworthy, in this study, iCCA cells were induced to generate NETs by binding to platelets through P-selectin [126]. These observations hint at the possibility that procoagulant and prothrombotic properties of NETs might represent a novel mechanism underlying the development of VTE, and thus may serve as a biomarker for the prediction of the VTE risk.

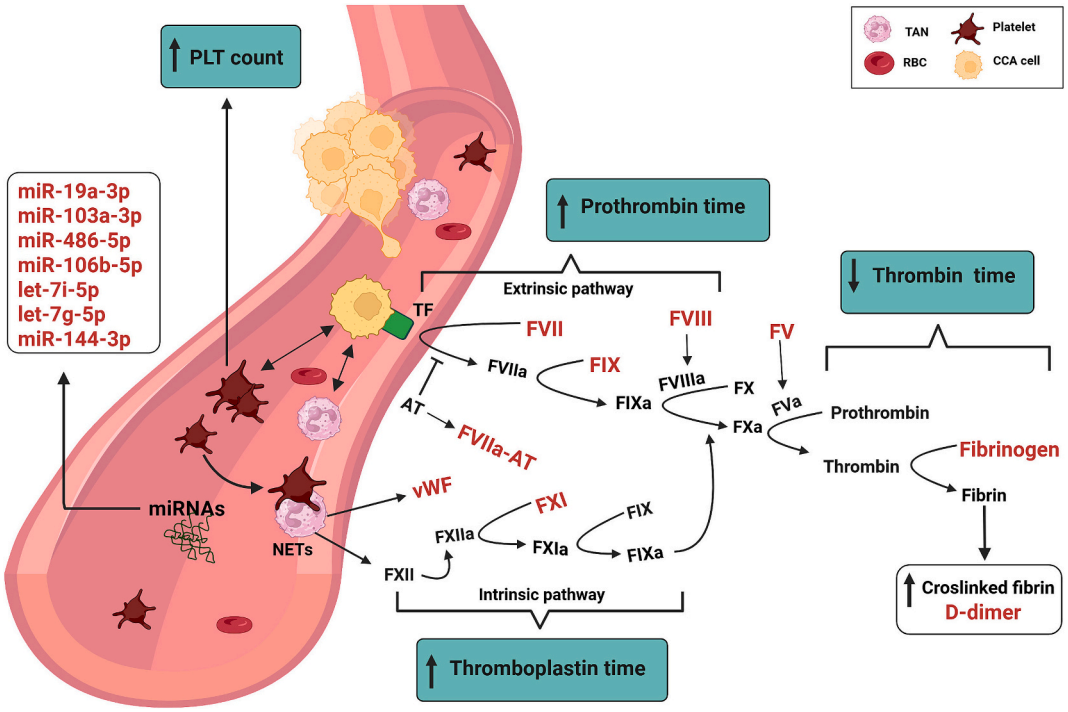


Fig. 3. Putative biomarkers relevant for different stages of pro-coagulant processes in CCA [39,40,139,140] (created in BioRender.com). Tumor cells in CCA express tissue factor (TF), which binds and activates factor VIIa (FVIIa), initiating the extrinsic coagulation cascade. This procoagulant activity is mediated by antithrombin (AT) through the formation of FVIIa–AT complexes, which elevated levels reflect persistent activation of the TF-dependent coagulation pathway. In addition, CCA cells interact with platelets, endothelial cells, and neutrophils, either via direct membrane contact or through paracrine signaling. Tumor-associated neutrophils can release neutrophil extracellular traps (NETs), which promote thrombosis by stimulating von Willebrand factor (vWF) secretion and by activating factor XII (FXII), thereby triggering the intrinsic coagulation pathway. CCA cells may also release circulating miRNAs with procoagulant properties, further contributing to the hypercoagulable state. Candidate biomarkers for VTE prediction are highlighted in red. Additionally, routine coagulation parameters, marked in green boxes, provide indirect evidence of coagulation system activation. These include elevated platelet count (PLT), activated partial thromboplastin time (aPTT), indicative of intrinsic pathway activity, and prothrombin time (PT), reflecting extrinsic pathway function. In contrast, thrombin time (TT), which assesses fibrinogen-to-fibrin conversion in the final step of coagulation, is typically reduced in this context. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

5.6. CCA-associated mucins (MUC)

Several lines of evidence suggest that mucins (MUCs), high molecular-weight surface glycoproteins produced in different types of cancers, with O-linked glycosylation sites acting as ligands for selectins [128], are putative molecular players of thrombogenesis. Through their ability to bind selectins, MUCs facilitate interactions between cancer cells and circulating blood cells, thereby promoting the development of microthrombi (Fig. 2) [128–130]. In ovarian and CRC cells, numerous MUCs, such as MUC1, MUC2, MUC4, MUC5AC, and MUC16, are upregulated [131,132], and in mucinous adenocarcinomas (e.g. PDAC), their circulating fragments are often detected in the serum of patients [133], providing the substrate for microthrombi generation [128]. CCA, especially the large-duct type, is characterized by an increased expression of mucins, such as MUC1, MUC2, MUC3, MUC4, MUC5AC, MUC6, MUC13, MUC15, and MUC16 [134,135]. Among them, MUC1 is the best characterized [136] and is reported as one of the more highly expressed mucins in CCA [134]. Interestingly, a case of Trousseau's syndrome in iCCA, was histologically characterized by the expression of MUC1 and MUC16 in the cytoplasm of tumor cholangiocytes [82]. Interestingly, human pancreatic and breast cancer cell lines expressed various procoagulant factors, such as TF, FV/FVa, FX/FXa, and thrombin, with levels positively correlating with those of MUC1, consistent with an active role in the pathogenesis of CAT [130]. Plausibly, mucins might play a pathogenic role in the development of thrombotic events also in CCA, where they are known to be associated with tumor progression and poor prognosis [134,135]. These observations lend support to the notion that in CCA, VTE development may indeed be regarded as a phenotype of a more aggressive tumor behavior.

6. Biomarkers for CCA-associated VTE and their possible utility to improve early detection of CCA

D-dimer, a cross-linked fibrin split product, is regarded in clinical practice as a marker of hemostasis activation and fibrinolysis (Fig. 3) [137]. When markedly elevated, serum levels of D-dimer are useful predictors of the development of VTE in cancer patients [138]. In CCA, D-dimer expression correlated with platelet count, CA19–9 serum levels, and patient clinical outcome, in terms of both tumor recurrence and poor survival [40,139]. Additionally, prolonged prothrombin time (PT) levels adversely affects survival of CCA patients who underwent curative surgery [39,140]. Similarly, high levels of fibrinogen, prolonged PT with increased international normalized ratio, prolonged activated partial thromboplastin time/ratio and shortened thrombin time, were associated with poorer prognosis in patients with biliary tract cancer after surgical resection (Fig. 3) [141]. Although the role of microRNAs (miRNAs) targeting the TF-driven extrinsic coagulation pathway has not been extensively studied in cancer-associated thrombogenesis, a set of plasma miRNAs (miR-19a-3p, miR-103a-3p, miR-486-5p, miR-106b-5p, let-7i-5p, let-7 g-5p and miR-144-3p) have been proposed to predict VTE events in CCA patients (Fig. 3) [142]. In addition, serum levels of procoagulant factors (FV, FVII, FVIII, FIX, FXI and vWF) have been found to correlate with the occurrence of CCA-associated VTE (Fig. 3) [143], though their predictive value needs further investigation.

Table 4
Cytokine and chemokine-mediated paracrine mechanisms originating from tumor cholangiocytes potentially inducing NET formation by acting on tumor-associated neutrophils in CCA.

CCA-associated stimuli	Molecular mechanism described	References
CXCL1, CXCL2, CXCL5, CXCL6 and CXCL8 (IL-8)	CXCR1- or CXCR2-mediated interactions induce NET formation in a concentration-dependent manner, promoting a NET-dependent protection mechanism of metastatic emboli from immune cytotoxic attacks.	[103,119–121]
IL1β	IL-1β induces NET formation and association with TF.	[103,116,121,122]
IL17	IL17/IL17RA axis promotes neutrophil recruitment into TME, induces NET formation and inhibits cytotoxic $CD8^+$ T cells against tumor cells.	[103,117,121,123,127]
IL33	IL33/IL33R axis induces neutrophil infiltration and NET formation	[103,117,118,121,124]

CCA-associated stimuli (first column) have been inferred from refs [103, 116–118] Their role in NET-formation, regardless of the CCA involvement, is supported by references related to other cancer types and inflammatory conditions, as reported in the third column [119–124,127].

Furthermore, CD24, a cell adhesion receptor acting as ligand of P-selectin, has been found frequently expressed by immunohistochemistry in tissue sections of iCCA patients (51 % of cases). In this regard, CD24 expression holds interesting functional significance. By binding to P-selectin, CD24 induced displacement of tumor cells in the endothelium [144], and stimulated interaction of leukocytes and platelets with the activated endothelial cells [145]. Further studies are needed to explore whether P-selectin ligands may serve as predictors for CCA-associated VTE [144].

Collectively, these findings highlight the current lack of sensitive and specific biomarkers for accurate prediction of the VTE risk in patients with CCA. However, given the urgent need of reliable biomarkers for the early detection of CCA, it is plausible that circulating factors or markers of coagulation activation might enhance the diagnostic accuracy of presently available, yet suboptimal, predictors, such as CA19–9 (Fig. 3). In this perspective, a recent study investigating the capacity of circulating EV-proteins to predict the risk of CCA, found fibrinogen associated with serum CRP and FRIL in the most powerful panel discriminating patients with early-stage CCA complicating primary sclerosing cholangitis (PSC) from those with PSC alone, even before clinical/radiological evidence of malignancy [146]. Starting from these observations, large prospective observational and experimental studies are sorely encouraged for defining risk stratification criteria essential for the generation of consensus guidelines of surveillance, prophylaxis and treatment. Issues on this theme are discussed below.

7. Thromboprophylaxis and treatment of CCA-associated VTE

Despite the advance in unravelling the pathophysiology of cancer-associated thrombosis, consensus guidelines specific to the prophylaxis and treatment of CCA-related VTE are still lacking. As aforementioned, a deeper understanding of the underlying mechanisms and a better definition of the patient-specific risk factors are indispensable to define the optimal approach. Notably, PSC is associated with a hypercoagulable state, as evidenced by thromboelastography, and may also be linked to abnormal platelet function [147]. Moreover, obstructive cholestasis, which often develops as early feature in CCA (particularly in pCCA and dCCA), is also associated with a procoagulant state and impaired fibrinolysis, despite a defective synthesis of vitamin K-dependent coagulation factors [148]. Anticoagulation remains the cornerstone of VTE treatment, after a thorough balance of the risks of bleeding. Current evidence suggests an integrated approach incorporating pharmacological agents such as low molecular weight heparin (LMWH) or direct oral anticoagulants (DOACs), tailored to individual risk profiles [149,150]. DOACs currently recommended for the treatment of cancer-associated thrombosis include the direct FXa inhibitors, apixaban, edoxaban and rivoraxaban [150,151]. However, although DOAC efficacy is well proven, they may increase the risk of gastrointestinal bleeding, in particular in patients with GI malignancies [152]. Thus, when DOACs are contraindicated because of a high gastro-intestinal bleeding risk (as reported for CCA patients with recurrent acute cholangitis), LMWH is strongly recommended. Nevertheless, data on the efficacy and safety of DOACs in the setting of CCA-related hypercoagulability remain limited compared to other malignancies [153]. Additional considerations, including the duration of anticoagulation therapy, potential interactions with systemic treatments, and the management of recurrent thrombotic events, are of paramount importance in optimizing clinical outcomes of patients with CCA-associated VTE. At present, routine prophylactic anticoagulation is not recommended in CCA. However, individualized assessment of thrombotic risk and consideration of primary prophylaxis may be warranted in select cases. In particular, for hospitalized patients with CCA, current guidelines for cancer patients recommend pharmacologic thromboprophylaxis with LMWH during hospitalization, to be discontinued upon discharge [150]. For CCA patients undergoing surgery, postoperative thromboprophylaxis with LMWH should be continued for at least 30 days after discharge [150], and early mobilization is preferred over mechanical prophylaxis. In patients with high thrombotic and bleeding risk, mechanical prophylaxis alone is initially recommended until bleeding risk subsides, after which pharmacological prophylaxis should be initiated [150]. In cancer outpatients receiving systemic therapy, current guidelines suggest thromboprophylaxis only for those deemed high-risk for VTE. However, according to the existing risk scoring systems [5,54], CCA is classified as an intermediate-risk tumor, complicating uniform decisions regarding prophylaxis. Recently, two placebo-controlled randomized clinical trials addressing the value of apixaban and rivaroxaban in preventive doses (2.5 mg twice daily and 10 mg once daily, respectively) for the prevention of VTE complications in cancer patients undergoing chemotherapy with a KRS $\geq$2 have been published. These studies support DOACs as effective and safe protective agents against VTE complications [154–156]. However, specific data on DOAC use for VTE prevention in CCA patients remain scarce. A randomized phase II open-label study (NCT03139487) compared the safety and efficacy of DOACs versus subcutaneous dalteparin in patients with various advanced GI malignancies, including biliary tract cancers. The study found that DOACs were associated with an increased bleeding risk compared to dalteparin, highlighting the need for extra caution when selecting anticoagulants in this particular clinical setting. In conclusion, collaborative efforts, including large-scale, disease-specific studies, such as the European Network for the Study of Cholangiocarcinoma (ENS-CCA), will be crucial for refining risk stratification models and optimizing treatment strategies for this understudied and high-risk population of cancer patients.

8. Conclusions

Occurrence of VTE is a feared complication of several epithelial cancers, including CCA, which incidence has sharply increased worldwide over the past two decades, also in young individuals. Epidemiological evidence indicates that VTE may reflect a more aggressive tumor phenotype, as it is independently associated with reduced survival in cancer patients, regardless of direct mortality from thrombotic events. Compared to other adenocarcinomas, such as PDAC and CRC, data on the association between CCA and VTE are relatively scarce. In particular, CCA patients have often been underrepresented in large cohort studies or when included, grouped into broader categories, such as “other GI cancers”, thereby limiting disease-specific analysis. As a result, CCA has

been rarely included explicitly in widely used VTE RAMs. Furthermore, many clinicians do not yet recognize CCA as a malignancy with a particularly elevated risk for VTE, despite emerging evidence indicates their close association, which is also supported by typical biological features of CCA. Among the several mechanisms underpinning cancer-associated thrombosis, pathways triggered not only by the malignant cells, but also by the TME, which is prominent in CCA, sustain blood hypercoagulability and endothelial activation. Importantly, TF can be released by CCA cells, to directly promote VTE by activating the extrinsic coagulation pathway. On the other hand, platelet adhesion and activation, together with NETs generated by TAN upon interactions with CCA cells within the TME, may contribute to procoagulant functions by activating the intrinsic pathway. In addition, other components of the TME, such as fibrosis, which is abundant in pre-malignant conditions, such as PSC, and frequently associated to PVT, might contribute to the activation of the coagulation cascade, a topic deserving consideration by future studies. Theoretically, since VTE is often an early manifestation occurring in the first 3 months from cancer diagnosis in about half of patients, CAT may be regarded either as a strategy adopted by the tumor to enhance its pro-invasive capabilities, or alternatively, as a long shot of the stromal reaction to erect a defense barrier against tumor spreading. Moreover, from a therapeutic perspective, the choice of anticoagulant therapy in CCA patients is challenged by the associated bleeding risk, which can be high in severe cholestasis. Overall, given the substantial risk of VTE in patients with CCA, further investigations are urgently needed to determine whether the universal thromboprophylaxis adopted in the cancer setting is safe and cost-effective. Indeed, future avenues to improve the benefit of VTE prophylaxis in CCA patients will be contingent on better methods to quantify the specific risk. In this regard, artificial intelligence and machine learning-based models may provide a comprehensive tool to predict VTE, potentially replacing traditional scoring systems with higher accuracy. Additionally, it will also be crucial to identify pathway-based biomarkers for an accurate prediction of CAT in CCA. This would be the pre-requisite to test, at least in a subset of patients, potentials of anticoagulation as a therapeutic resource in the fight against a worrisome cancer, still short of curative approaches.

Declaration of competing interest

(Luca Fabris reports financial support was provided by PRIN 2022AHM4AA. Luca Fabris and Massimiliano Cadamuro are members of COST Action CA22125 “Precision medicine in biliary tract cancer (Precision-BTC-Network).” If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.)

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Data availability

No data was used for the research described in the article.

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