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Venous thrombosis associated with pancreatic cancer

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ABSTRACT

Introduction. Cancer-associated thrombosis is a significant prognostic marker in pancreatic neoplasia, with a venous thromboembolism incidence of 17-34%. This study focuses on cancer-associated thrombosis risk factors, screening scores, and treatment options. *Materials and Methods*. Comprehensive database searches were conducted across Web of Science, PubMed, Reaxys, ScienceDirect, and Scopus. *Results*. Of the 37 articles reviewed, findings include splanchnic vein thrombosis correlating with pancreatic complications and survival rates. Gender differences in cancer-associated thrombosis risk were inconclusive, while African Americans showed a higher incidence of pulmonary embolism. Various cancer-associated thrombosis staging scores were evaluated, with ONKOTEV score outperforming Khorana. Direct oral anticoagulants were suggested as viable alternatives to low molecular weight heparins. Non-anticoagulant sulfated low molecular weight heparin emerged as a future option, offering reduced bleeding risks with similar efficacy. *Conclusions*. Managing cancer-associated thrombosis in pancreatic cancer is challenging, highlighting the need for improved understanding, better screening methods, and more effective treatments.

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Introduction

Cancer-associated thrombosis (CAT) is a hazardous connection between two pathologies with great mortality and morbidity. The prognosis of their association varies with factors such as localization of the primary tumor, type of treatment (surgical or chemotherapy), presence of metastasis or other comorbidities [1]. The risk of venous thromboembolism (VTE) is four times higher in malignant compared to non-malignant patients, with pancreatic cancer (PC) having the highest incidence of VTE (between 17−36%) [2,3].

PC has numerous mechanisms which sustain the high rate of VTE incidence, such as high levels of tissular factor (TF), associated with microparticles or endosome vesicles derived from malignant cells, secretion of MUC1 protein or presence of CA19.9 antigen [4]. There are concerns about the rise of CAT cases, with Mahajan et al. stating that there is a significant increase of cumulative pulmonary embolism (PE) and deep vein thrombosis from 55.7% between 2005-2007 to 60.5% between 2014-2017 [5]. In an analysis of 28,468 patients with active cancer who had an episode of VTE between 2014 and 2019, more than 50% did not receive any outpatient anticoagulant therapy within 30 days of VTE event, exposing them to a great risk because patients with active cancer have a higher risk of recurrent VTE, with a worse overall survival (OS) than patients under anticoagulant treatment [6]. Søgaard et al. showed that the survival rate at 3 months for patients with pancreatic adenocarcinoma was 35% when presenting VTE vs. 53% without VTE (95% CI, 0.8–2.9) [7]. Low molecular weight heparins (LMWH) were long-time considered the best treatment for these patients, with studies revealing a survival advantage [8]. However, after the appearance of direct oral anticoagulants (DOACs) in 2010s, they were finally included in the 2020 American Society of Clinical Oncology guidelines, recommending rivaroxaban, apixaban or edoxaban in patients with CAT.

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Materials and Methods

A careful analysis of the literature was done using databases such as Web of Science, PubMed, Reaxys, ScienceDirect and Scopus. To enhance the precision of our research, we have developed an advanced search formula designed to uncover the most relevant and comprehensive data: ("risk" AND "factors") OR "risk factors") AND ("therapeutics" OR "therapeutics" OR "treatments" OR "therapy" OR "therapy" OR "treatment" OR "treatments") AND ("thrombose" OR "thrombosing" OR "thrombosis" OR "thrombosis" OR "thrombosed" OR "thromboses") AND ("associated") AND ("pancreatic neoplasms" OR ("pancreatic" AND "neoplasms") OR "pancreatic neoplasms" OR ("pancreatic" AND "cancer") OR "pancreatic cancer". The most relevant articles published between 2008-2023 were selected. For "risk factors", articles with significant statistics in one of the three major pools were included: factors pertaining to the patient (sex, ethnicity, age, body mass index (BMI), presence of other comorbidities etc.), factors pertaining to the disease itself (cancer type, stage of cancer, location of VTE, recurrence of VTE etc.) and factors pertaining to treatment (type of surgical treatment, chemotherapy, comparisons between DOACs, LMWH and Warfarin, immobilization after surgery). Furthermore, different scores for CAT in clinical practice were evaluated, such as Khorana, Vienna, Ottawa, ONKOTEV Score and their role in this analysis. Regarding the pathophysiological factors associated with PC, both in vivo and in vitro studies were included. This analysis included 37 articles, presenting the results of important trials such as *"Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer" (CARAVAGGIO), "Apixaban and dalteparin in active malignancy associated venous thromboembolism" (ADAM-VTE), "Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D)" (SELECT-D), "Semuloparin for Thromboprophylaxis in Patients Receiving Chemotherapy for Cancer" (SAVE ONCO), "A Randomized Double-Blind Placebo-Controlled Study on Nadroparin for Prophylaxis of Thromboembolic Events in Cancer Patients Receiving Chemotherapy: The PROTECHT Study" (PROTECHT), "Efficacy of Prophylactic Low-Molecular Weight Heparin for Ambulatory Patients With Advanced Pancreatic Cancer: Outcomes From the CONKO-004 Trial" (CONKO-004) and "Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer" (CASSINI).* The comparison between these studies dictated the protocols followed nowadays in international guidelines and gave a consensus for the dilemma of choosing the optimal treatment in different complex situations. The most important factor in the selection of the articles was their correlation and presence of statistics pertaining to PC. Thus, studies which offered non-significant information to CAT in PC were excluded.

Discussions

The mechanisms of CAT in PC

In patients with PC, studies have shown increased levels of tissue factor (TF) and the release of TF + microvesicles (MVs) in the circulation [9]. It was observed that ovarian, brain and pancreatic tumors are associated with high levels of TF, leading to a higher incidence of VTE [9]. It has been suggested that the interference of TF-dependent signal transduction can be a target for treatment alongside the inhibition of platelet activation. Elevated TF-MVs activity was linked with an unfavorable prognosis. However, TF expression in malignant cells was not correlated with plasma TF-MVs activity, suggesting that macrophages are another source of TF-MVs activity [4]. Clopidogrel was found to reduce the levels of TF-MVs in mice, suggesting a possible role of preventing VTE in cancer patients [10]. A study that included 11 PC patients concluded that a time-dependent increase in TF-MVs levels was present before the incidence of VTE, suggesting the possibility of a screening method in clinical practice using TF-MVs serum tests [10]. Another recent study by Kobayashi et al. demonstrated that high levels of plasma TF are an important predictor for the risk of VTE in PC patients who already have a high Khorana Score >3 or high D-dimer levels [11].

Pancreatic adenocarcinoma (PADC) is a mucin-producing tumors, which together with lung and gastrointestinal adenocarcinoma, have higher risk of association with VTE [12]. It was postulated that MUC1, a transmembrane glycoprotein, may also play an important role in the initiation and aggravation of thrombosis [4]. The structure of these factors can be modified by the action of CA19-9 or sialic Lewis antigen, another important factor associated with a worse prognosis [13]. Krepline et al. demonstrated that the increase of CA19-9 levels after adjuvant therapy or before surgery (HR:1.97; 95%CI:1.27–3.04; P=0.002) was an independent negative risk factor in PC patients [14].

The difference between asymptomatic and incidental CAT

The VTE in PC is not always symptomatic. Hicks et al. conducted a trial of 95 patients and observed that all VTEs were diagnosed incidentally, meaning that their discovery was unrelated to the clinical manifestations [3]. The subcommittee of Hemostasis and Malignancy of the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) advised using the term "incidental" and "not asymptomatic" because this event is a symptom of the

cancer itself [15]. An interesting recommendation was made by the American College of Chest Physicians (ACCP) guidelines that symptomatic VTE should be treated with anticoagulants, whereas incidental VTE in asymptomatic patients should receive no anticoagulant therapy [15]. These recommendations are not in line with other studies that suggested the use of anticoagulants because of the higher risk of mortality and recurrence posed by a first VTE episode [6,16]. The literature shows that the most common manifestations of VTE in PC are deep vein thrombosis and pulmonary embolism, but recently it was noted that incidental episodes of PE and visceral vein thrombosis are increasing, being responsible for almost 50% of all reported events [17].

The unfavorable and frequent location of VTE

Regarding the visceral site of VTE, it is most frequently found in splanchnic veins, with the highest incidence in portal vein, followed by mesenteric vein and splenic vein, with an overall poor prognosis [3,18]. In a systematic review of Dedania et al., the authors have found that splanchnic vein thrombosis is associated with more severe intraoperative hemorrhages, pancreatic complications and a worse survival [15,19]. Furthermore, splanchnic vein thrombosis represents an important early sign of malignancy, found in liver cancer and PC, with a diagnosis of malignancy three months after the event in one study [20]. The clinical manifestations of splanchnic vein thrombosis are related to portal hypertension and even ascites. A recent study showed that ascites was present in 83% of the cohort of PC patients [21]. Regarding the prognosis, another study analyzed 122 patients with splanchnic vein thrombosis and concluded that this factor increased one year mortality by two folds (adjusted hazard ratio (aHR) 2.02, 95% confidence interval (CI) 1.65–2.47 [22]. Furthermore, anticoagulant treatment did not increase the survival rate of patients, but led to a higher risk of hemorrhage [22].

The dangerous association between VTE and PC

VTE associated with PC has a higher incidence than in other malignancies. Sargam et al. conducted a study which underlined the 10-fold higher risk of PC-associated VTE at 180 days, compared to patients with no prior VTE episode (36.9% vs 3.66%; 95% CI 15.22-15.6, P value <0.0001) [16]. An interesting observation was that while the risk of VTE depends on the type of malignancy, with PC having the highest risk of 10.5%, the incidence of recurrent episodes in patients with prior VTE was similar for all malignancies [16]. The stage of malignancy has an important impact on the occurrence of VTE in PC patients. For example, in stage IV PC, it is 4 times more likely for VTE to reoccur (HR, 3.8;95% CI, 1.68-8.58; P=0.001), than other stage IV malignancies [23]. Furthermore, Mahajan et al. reported an almost three-fold increase in CAT incidence for stage IV and almost two-fold increase for stage II/III in pancreatic malignancy compared to stage I, however with a p-value of 0.0594 [5].

Treatment, ethnicity and cancer stage

Two important treatment lines in PC are surgery and chemotherapy. In general, the incidence of VTE is 6.5 times higher with chemotherapy whereas in surgical treatment it is two times higher, compared with non-cancer patients [9]. In PC, in comparison to other types of malignancies, gender was not associated with a higher or lower risk of CAT, demonstrating that both genders are equally affected by this disease [5].

It was observed in numerous studies that ethnicity may play an important role in the incidence of VTE. In a cohort of 38,431 persons with different races, African Americans had the highest incidence for PE (5-7%), followed by Caucasian and Hispanic population, whereas Asian/Pacific population recorded the lowest incidence (2.5%-3.6%) [24]. However, further studies need to include this parameter in a risk prediction model for CAT [24,25]. The stage of malignancy (stage IV) is another important factor with survival rate lower than 10% at 5 years after diagnosis [17]. Numerous studies stated that one of the most important predictors for CAT is the presence of metastasis [1,17]. The risk of CAT is not different in PC patients under distinct chemotherapeutic regimens [26]. Vadhan-Raj et al. studied a subgroup of 273 PC patients included in CASSINI trial and found no difference in the incidence of VTE in patients treated with 5-fluorouracil-based regimen compared to gemcitabine-based regimen [26].

In the case of recurrent VTE, Vedovati et al analysed the CARAVAGGIO trial and showed that a higher DVT index (HR 1.77, CI 1.21–2.58), Eastern Cooperative Oncology Group (ECOG) status of 1 or more (HR 2.06, CI 1.29–3.30), pancreatic or hepatobiliary cancer (HR 2.62, CI 1.57–4.36), anti-cancer treatment during the study period (HR 2.49, 1.42–4.34) were associated with a two fold higher risk compared to a control group [27].

Another study found that the elevation of factor VIII, D-dimers, tissue factor-dependent procoagulant activity of MP (TF-MP), tissue factor pathway inhibitor (TFPI), and extracellular DNA were related to the cancer process and not to inflammation, differentiating pancreatic cancer from chronic pancreatitis. Additionally, the study found that D-dimers were associated with the occurrence of future VTE in pancreatic cancer patients. It is important to note that these findings are based on the available studies and further research may be needed to confirm these protective factors [28].

Protective predictors

In a study conducted by Hanna-Sawires et al., the authors analyzed a cohort of 361 patients with PC over a period of 43 months. One of the conclusions was that

biliary drainage (HR 0.52, 95%CI 0.28–0.98) and tumor resection (HR 0.45, 95%CI 0.45–1.83) were protective factors for VTE [29]. Furthermore, one study has found that Rh antigen positivity is another protective factor for VTE through an unknown mechanism, calling for further studies [14]. Finally, the most important findings for risk factors and protective factors were organized and presented (Table 1).

Table 1. Pancreatic cancer-associated thromboembolism; risk factors and protective factors

Worse Prognosis	*Protective Predictors*
Increased Tissular Factor	Tumor resection
Presence of MUC1	Biliary drainage
Presence of CA 19-9	Rh (+) antigen
Splanchnic vein thrombosis	Asian/Pacific population
Recurrent Venous Thromboembolism	
African/American population	
Stage IV Cancer	

Score systems

The need to quantify the risk factors of CAT led to the introduction of different score systems, starting with Khorana score which evaluated five factors: site of cancer, erythropoiesis stimulating agents, platelet count, leukocyte count and BMI [30]. Khorana score presents 3 categories for the risk of symptomatic VTE: low (0 points), intermediate (1-2 points) and high-risk (minimum 3 points). PC and stomach cancer were considered "very high risk" malignancies, with a minimum score of 2 points [9]. However, there are some limitations with this model, because for patients with intermediate and high-risk scores there was no difference in the incidence of VTE (in lung and pancreas malignancy), leading to a poor capacity of discrimination between low-risk and high-risk patients [13]. Other drawbacks of Khorana score are the lack of a parameter assessing previous VTE episodes or presence of a hypercoagulable state, factors which are important in the decision of anticoagulation treatment. It was postulated that CA19-9 can be introduced in risk stratification models.

More recently, other risk scores were created, with ONKOTEV score showing promising results (Table 2). In a cohort of 165 patients with PC, the cumulative VTE incidence of 3.3%, 12.7%, 50.9%, and 82.4% was correlated with ONKOTEV scores of 0, 1, 2, and ≥3, respectively ($p < 0.001$) [31]. Furthermore, patients eligible for anticoagulant treatment had an ONKOTEV score ≥2, with a major hemorrhage risk of less than 2%. The proposed tool presents 4 factors which improve the predictability of Khorana score: presence of metastatic disease, compression of vascular/lymphatic structures, history of previous VTE and Khorana score of ≥2 [31].

Table 2. ONKOTEV Score

Risk Factors	*Score*
Khorana Score	1
Presence of metastases	1
Vascular/Lymphatic compression	1
Previous Venous Thromboembolism	1

Total Score:

Score 0 = low risk
Score 1-2 = intermediate risk
Score > 2 = high risk

A comparison between DOACs and LMWH

With the appearance of DOACs in 2010s, a heated debate started on the optimal treatment for CAT, to lower the risk of VTE. Recent studies concluded that there is not optimal safe strategy for treating CAT, but rather a personalized “best fit” strategy which needs to address different important factors: type of cancer, presence of metastasis, history of VTE, risk of bleeding or patient preference [32].

Interestingly, in a survey of 100 patients conducted by Noble et al., the main concerns for patients whether to receive anticoagulant treatment were the interaction between anticoagulants and other medications (39%), efficacy of VTE treatment (24%) and major haemorrhage risk (19%), with the method of anticoagulant administration having a lower importance (13%) [33].

A systematic review and meta-analysis from 2020 made comparisons between DOACs and LMWH in terms of efficiency in preventing VTE, recurrent VTE and overall survival [34]. It analysed 4 trials, including CARAVAGGIO, ADAM-VTE, SELECT-D trials and found that there is no notable evidence supporting the superiority of one of these treatments, with one exception: DOACs (Apixaban, Edoxaban, Rivaroxaban) slightly decreased the risk of developing VTE or recurrent VTE and only Edoxaban had an increased risk of major bleeding compared to LMWH (Dalteparin) [34]. In a study by Costa et al. with over 1050 CAT patients treated with LMWH (mostly enoxaparin) or rivaroxaban, the latter was associated with a reduced incidence of recurrent VTE in comparison to LMWH without an important risk of major hemorrhage or mortality, making it an important alternative for LMWH for CAT [35].

Finally, Frere’s study analyzed the most important trials conducted from 2010 to 2021 which compared DOACs and LMWH and presented a step-based approach in which LMWH is considered the primary solution for initial and long-term treatment of VTE when creatinine clearance is ≥ 30 ml/min. Rivaroxaban or edoxaban can be an alternative solution when the patient does not present a risk of

gastrointestinal or genitourinary bleeding or when LMWH are contraindicated. Regardless of the treatment for CAT, there is a lack of evidence related to an improvement of survival rate, calling for further studies [9,17,22,29,34].

A promise for the future: Sulfated non-anticoagulant low molecular weight heparin

With the necessity of a better thromboprophylaxis of CAT, recent studies conducted on mice and rabbits led to the discovery of heparin derivates with a lot of potential. Sulfated non-anticoagulant low molecular weight heparin (S-NACH) has a different mechanism of action compared to LMWH: it doesn't interfere with the activation of FX or FII, but rather potentate the activity of tissue factor pathway inhibitor, leading to a reduced risk of bleeding complications. S-NACH has advantages because of two reasons: PC is associated with high levels of TF, and S-NACH can solve the problem of other CAT treatments – major bleeding risks. In a study conducted by Darwish et al., a comparison between LMWH (enoxaparin and tinzaparin) and S-NACH was made on mice and rabbits. While LMWHs were associated with an increased haemorrhage time, S-NACH bleeding time was comparable to control [36].

Conclusions

The management of VTE in patients with PC continues to be a challenge because of the high mortality and morbidity of the disease. However, with a better understanding of the pathology, the introduction of more performant methods of screening, better assessment scores and lines of treatment, physicians will be able to evaluate the status of a patient more correctly and decide the type of treatment best suited for the patient. With updated guidelines that include DOACs and promise for better alternatives like S-NACH, the safety of the patient will increase, while decreasing the burden of CAT in PC patients.

Highlights

- ✓ The prognosis of pancreatic cancer associated with thrombosis varies with factors such as localization of the primary tumor, type of treatment (surgical or chemotherapy), presence of metastasis or other comorbidities.
- ✓ Important risk factors that should be mentioned are increased levels of Tissular Factor, presence of MUC1 and CA19-9 markers, recurrent thrombosis episodes, African/American population or stage IV cancer.
- ✓ With the introduction of ONKOTEV score, the risk of thrombosis can be evaluated more accurately with an important role in the choice of treatment.

Abbreviations

CAT	:	Cancer-associated thrombosis
VTE	:	Venous thromboembolism
PC	:	Pancreatic cancer
PE	:	Pulmonary embolism
TF	:	Tissular factor
OS	:	Overall survival
LMWH	:	Low molecular weight heparins
DOACs	:	Direct oral anticoagulants
MVs	:	Microvesicles
PADC	:	Pancreatic adenocarcinoma
SSC	:	Subcommittee of Hemostasis and Malignancy of the Scientific and Standardization Committee
ISTH	:	International Society on Thrombosis and Haemostasis
ACCP	:	American College of Chest Physicians
aHR	:	Adjusted hazard ratio
CI	:	Confidence interval
ECOG	:	Eastern Cooperative Oncology Group
TF-MP	:	Tissue factor-dependent procoagulant activity of MP
TFPI	:	Tissue factor pathway inhibitor
S-NACH	:	Sulfated non-anticoagulant low molecular weight heparin

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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