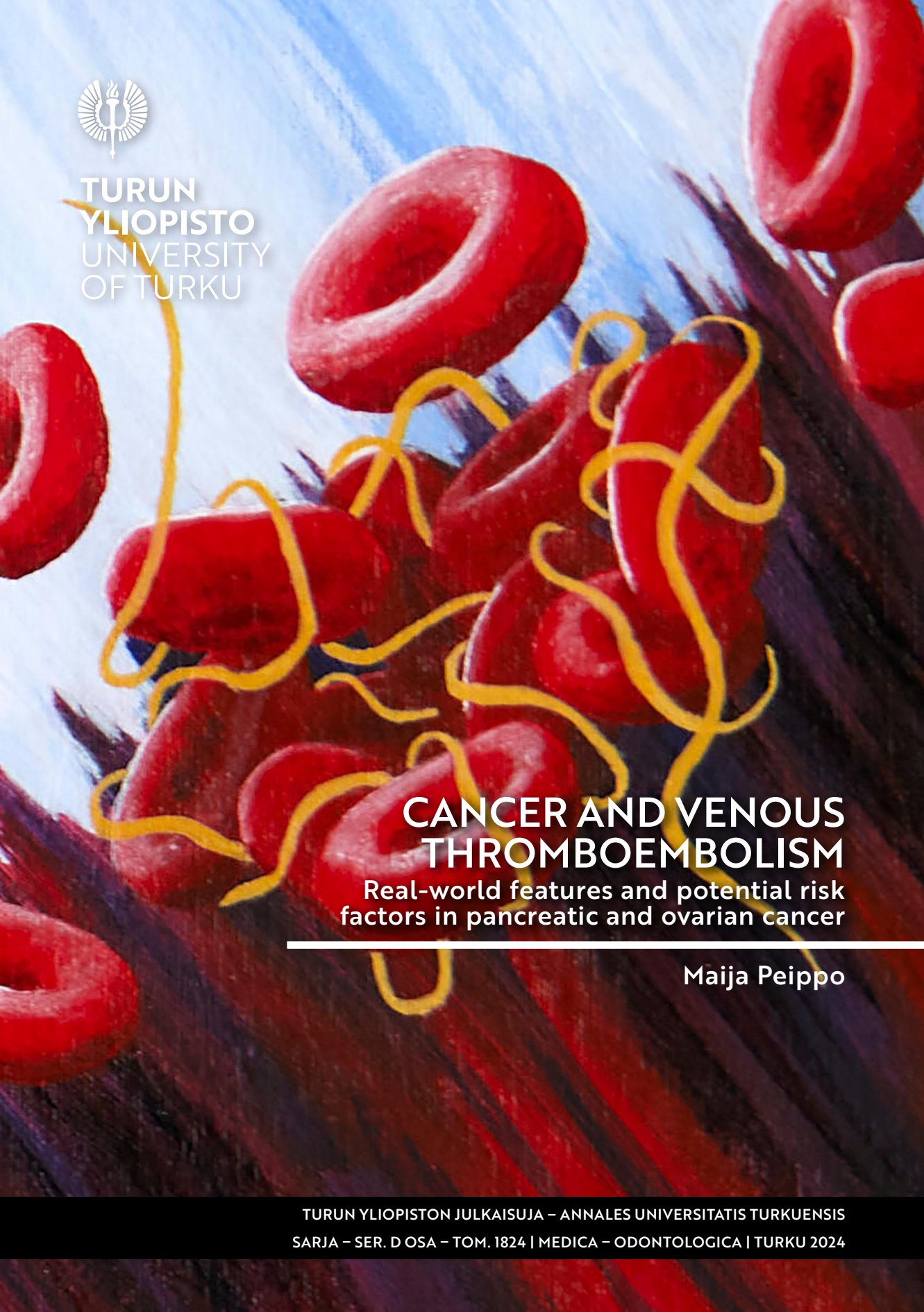

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Real-world features and potential risk factors in pancreatic and ovarian cancer

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”Kaikki ruoskivat toiveet, kaikki päättämättömyys,
ovat lopulta tarkoituksen palasia,
osa arvoitusta ja osa totuutta”
(Toni Wirtanen)

Isälleni

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ABSTRACT

Venous thromboembolism (VTE) contributes to morbidity and mortality although it is a treatable and even potentially preventable medical condition. The clinical manifestations of VTE vary from asymptomatic deep venous thrombosis (DVT) to potentially fatal pulmonary embolism (PE). Cancer is the main risk factor for VTE, and the incidence of cancer-associated thrombosis has increased during the last decade. VTE causes distress to cancer patients, interrupts and often delays anticancer therapy and increases morbidity, as well as general healthcare costs.

The association between cancer and venous thrombosis has been known for over a century. However, it is unclear how malignancy affects the hemostatic system and if VTE events could be predicted. It is challenging to know who will gain from preventative treatment of VTE and who will suffer from complications of anticoagulant therapy. Therefore, it would be valuable to identify potential clinical markers to predict VTE. If cancer patients with a considerable VTE risk were better recognized, individual thromboprophylactic approaches would be easier to design.

This study was designed to investigate the real-world incidence of VTE in a large hospital cohort and to evaluate, whether clinical and laboratory variables used in routine clinical care could predict VTE in cancer patients, especially in those with pancreatic cancer (PC) or high-grade serous ovarian cancer (HGSOC). We utilized the ability of a Finnish biobank to combine internationally unique real-world clinical data from different electronic health records. The overall aim was to find factors that could be used in clinical decision-making for VTE risk assessment among cancer patients.

In our study, about a quarter (26.9%) of patients with VTE had a concurrent cancer diagnosis. The highest VTE risk was associated with pancreatic, lung and ovarian cancer. During chemotherapy, VTE risk was increased among patients on platinum-based chemotherapy and those with elevated neutrophil counts. In patients with PC, short doubling time of the tumor marker CA 19-9 (CA 19-9-DT) significantly predicted VTE risk. Among patients with HGSOC, higher tumor marker CA 12-5 was associated with the risk of VTE, as well as a poor response to platinum-based cancer treatment.

KEYWORDS: Venous thromboembolism, cancer, predictive biomarker, pancreatic cancer, high-grade serous ovarian cancer, real-world data

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TIIVISTELMÄ

Syöpä on syvän laskimotukoksen merkittävä riskitekijä ja viime vuosikymmenten aikana syöpään liittyvien laskimotukosten määrä on lisääntynyt. Kyseessä on hoidettavissa ja jopa ehkäistävissä oleva sairaus, joka kuitenkin lisää sekä sairastavuutta että kuolleisuutta. Kliininen ilmentymä vaihtelee oireettomasta laskimotukoksesta jopa äkkikuolemaan johtavaan keuhkovaltimotukokseen. Syvä laskimotukos heikentää elämänlaatua, viivästyttää syöpähoitoja sekä lisää hoitokustannuksia ja kuolleisuutta. Syöpäpotilaiden yleisin kuolinsyy itse syövän jälkeen on syvä laskimotukos.

Syövän ja syvän laskimotukoksen välinen yhteys on tunnettu jo vuosisadan ajan. Silti edelleen tutkitaan sitä, miten syöpä vaikuttaa hyytymisjärjestelmään ja voidaanko syöpäpotilaiden laskimotukostapahtumia ennustaa. Haasteena syöpähoitojen kehittyessä on tunnistaa ne tukosalttiit potilaat, jotka hyötyisivät ennaltaehkäisevästä veren hyytymistaipumusta vähentävästä lääkityksestä. Toistaiseksi kliinisessä käytössä ei ole riittävän toimivaa syöpäpotilaan tukostapahtumaa ennustavaa mallia.

Väitöskirjatutkimuksen tavoite oli selvittää syvien laskimotukosten esiintyvyyttä syöpää sairastavilla ja sitä, voidaanko kliinisten tekijöiden ja laboratoriokoetulosten pohjalta arvioida laskimotukoksen riskiä, etenkin haima- ja munasarjasyöpäpotilailla. Tutkimuksessa hyödynnettiin suomalaisen biopankin toimintaa, joka mahdollistaa terveydenhuollon sähköisten potilastietojen yhdistelemisen ja tosielämän tutkimustiedon tuottamisen. Tavoitteena oli löytää tekijöitä, joita voitaisiin jatkossa käyttää arvioitaessa syöpäpotilaan laskimotukoksen riskiä ja tukoksia ehkäisevän lääkityksen tarvetta.

Tutkimuksessa todettiin, että syvään laskimotukokseen sairastuneista joka neljännellä (26.9%) oli samanaikaisesti myös syöpädiagnoosi. Suurin laskimotukoksen riski liittyi haima-, keuhko- ja munasarjasyöpään. Riskiä lisäsivät myös platinapohjainen solunsalpaajahoito ja veren kohonnut neutrofiilitaso. Haimasyöpäpotilailla kasvainmerkkiaineen CA 19-9 lyhyt kahdentumisaika ennusti merkittävästi tukosriskiä. Korkea-asteista seroosia munasarjasyöpää sairastavilla potilailla syvän laskimotukoksen riski liittyi kasvainmerkkiaineen CA 12-5 korkeaan pitoisuuteen ja huonoon vasteeseen platinapohjaiselle syöpähoidolle.

AVAINSANAT: Syvä laskimotukos, syöpä, ennustetekijä, haimasyöpä, korkea-asteinen seroosi munasarjasyöpä, tosielämän tieto

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Abbreviations

AI	Artificial intelligence
aPTT	Activated partial thromboplastin time
BMI	Body mass index
bpm	Beats per minute
BRCA	Breast cancer gene
CA 12-5	Carbohydrate antigen 12-5
CA 19-9	Carbohydrate antigen 19-9
CAT	Cancer associated thrombosis
CEA	Carcinoembryonic antigen
Cl	Confidence interval
COMPASS	Comparison of methods for thromboembolic risk assessment with clinical perceptions and awareness
COVID-19	coronavirus disease 2019
CT	Computed tomography
DOAC	Direct oral anticoagulant
DT	Doubling time
DVT	Deep venous thrombosis
e.g.	*Exempli gratia*, from example
eGFR	Estimated glomerular filtration rate
et al.	*Et alii,* and other
EHR	Electronic health record
EOC	Epithelial ovarian cancers
ESA	Erythropoiesis stimulating agents
ETMK	Ethics committee of the hospital district of Southwest Finland
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasound
FDA	United States Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FOLFIRINOX	Leucovorin (Folinic acid)- 5-fluorouracil-irinotecan-oxaliplatin
G-CSF	Granulocyte colony stimulating factor
HE4	Human epididymis protein 4

HGSOC	High-grade serous ovarian cancer
HR	Hazard ratio
ICD	International classification of diseases
ICD-10	International classification of disease 10th revision
IDS	Interval debulking surgery
i.e.	*Id est*, that is
IXa	Activated IX
LMWH	Low-molecular weight heparin
MRI	Magnetic resonance imaging
NA	Not assessed
NACT	Neoadjuvant chemotherapy
NCSP	Nordic classification of surgical procedures
NETs	Neutrophil extracellular traps
NR	Not reported
OC	Ovarian cancer
OS	Overall survival
PARP	Poly ADP-ribose polymerase
PC	Pancreatic cancer
PDS	Primary debulking surgery
PE	Pulmonary embolism
PFI	Platinum-free-interval
PROTECHT	Prophylaxis of thromboembolism during chemotherapy
pTNM	Pathological tumor-node-metastasis
PVT	Portal vein thrombosis
RAM	Risk assessment model
RECIST	Response evaluation criteria in solid tumors
ROC	Receiver operating characteristic
RR	Relative risk
RWD	Real-world data
s.c	Subcutaneously
SNOMED	Systematized nomenclature of medicine
TF	Tissue factor
THL	Finnish Institute for Health and Welfare
TNM	Tumor-nodes-metastasis
TYKS	Turku University Central Hospital
Va	Activated V
VEGF	Vascular growth factor
Vienna-CATS	Vienna cancer and thrombosis study
VIIa	Activated VII
VKA	Vitamin K antagonist

VTE	Venous thromboembolism
WHO	World Health Organization
Xa	Activated X
XIa	Activated XI
XIIa	Activated XII

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Peippo MH, Kurki S, Lassila R, Carpén O. Real-world features associated with cancer-related venous thromboembolic events. *ESMO Open,* 2018; 5: e000363-000363.

II Peippo MH, Kurki S, Seppänen H, Lassila R, Carpén O. CA 19-9 doubling time in pancreatic cancer as a predictor of venous thromboembolism. *Acta Oncologica*, 2019; 2: 237-241.

III Peippo MH, Perkonoja K, Isoviita V-M, Hynninen J, Lassila R, Carpén O. Association of clinical and laboratory variables with venous thromboembolism risk in high-grade serous ovarian cancer. *Manuscript.*

1 Introduction

Venous thromboembolism (VTE) is a heterogeneous group of diseases that commonly include abnormalities in blood flow (stasis), the blood itself (hypercoagulability), and in endothelial cells lining the blood vessels (endothelial injury). This phenomenon is known as the Virchow's triad. [1] The common manifestations of VTE are deep venous thrombosis (DVT), most often involving lower extremities, and pulmonary embolism (PE). VTE is a major health problem associated with increased morbidity and mortality [2–4] and it is approximately the third most common cause of vascular mortality worldwide [5]. Although VTE is a treatable and potentially preventable medical condition, the clinical manifestations vary from asymptomatic DVT to potentially fatal PE [6].

Every fifth patient with VTE has a concurrent malignancy, and 5% of patients are diagnosed with cancer during the first year after VTE [7–10]. Therefore, cancer is one of the main risk factors for VTE [11,12]. In particular, multiple myeloma and adenocarcinomas, e.g. pancreatic and ovarian cancer, are malignancies with the highest incidence of VTE [13].

VTE causes distress to cancer patients [14,15], interrupts and often delays anticancer therapy and is a significant cause of morbidity. It also increases general healthcare costs. [16,17] Moreover, VTE is the leading cause of death in cancer patients after the cancer itself [18].

Routine VTE prophylaxis cannot be recommended for all cancer patients as anticoagulant treatment enhances bleeding tendency [19,20]. However, VTE prophylaxis should be considered for carefully selected high-risk patients. In recent years, studies have focused increasingly on the prevention of VTE in cancer outpatients during systemic anticancer therapy. While anticoagulants decrease VTE incidence among cancer patients, they also increase the risk of major bleeding complications. [21–23] This is probably the reason why survival rates have not improved as expected.

Predictive markers are needed to identify which cancer patients would benefit from thromboprophylaxis therapy and which patients are more likely to experience the side-effects (bleeding etc.). A variety of biomarkers have been specifically investigated for their capacity to prefigure VTE among cancer patients. Also, various

risk assessment models have been developed for this purpose. A few variables such as elevated leukocyte and platelet count and decreased hemoglobin level seem useful for VTE risk prediction during chemotherapy. [24] However, more sensitive risk models and better predictive markers are still needed.

The hypercoagulable state varies by different cancer types and leads to cancer dependent variations in the risk of VTE. Pancreatic cancer (PC) and ovarian cancer (OC) are malignancies with the highest incidence of VTE. [25–27] Cells of these cancer types express tissue factor (TF) and release TF in the form of microparticles into the circulation. This activates the clotting system and increases the risk of VTE events. [28–33]

VTE is associated with poor prognosis and it increases mortality in both PC and high-grade serous ovarian cancer (HGSOC) [34–40]. By identifying potential clinical markers to predict VTE, PC and HGSOC patients with a considerable VTE risk could be better recognized. Individual thromboprophylactic approaches could be designed to prevent deterioration in patients' quality of life, and to ultimately extend survival and reduce healthcare costs.

2 Review of the Literature

2.1 Venous thromboembolism (VTE)

Thromboembolic diseases can be divided into arterial and venous thrombotic conditions. VTE and the major arterial thromboses, including ischemic heart disease and ischemic stroke, were considered different diseases until the 21st century. Studies have since concluded that these two thrombotic conditions are associated with each other [41,42] and have several similar risk factors [43,44]. In the current thesis, VTE was defined as deep venous thrombosis (DVT) in the lower or upper extremities or pulmonary embolism (PE). Also, rare thromboses in the veins of abdominal viscera (including portal vein thrombosis (PVT), mesenteric thrombosis and splenic thrombosis) [45,46] were included.

2.1.1 Epidemiology

VTE is the third most common cardiovascular disease after myocardial infarction and stroke in the Western Countries [47]. The overall annual incidence in Europe and the United States varies from one to two per 1000 people and 300 000 to 600 000 individuals [2,7,8,48–51]. The actual incidence might be even higher because of undiagnosed VTE events [52]. The incidence of DVT is double that of PE [53]. In clinical practice, two thirds of the VTE events are DVTs and only one of third are PEs (with or without DVT) [51,54].[6]

The incidence rates of VTE vary by age, race, and gender as **Table 1** shows. The highest VTE incidence is seen among patients 80 years of age or older [49–52,55]. Men have a slightly higher incidence compared to women [56]. However, the rates of VTE are higher in women below 50 years of age than men of the same age [52] which may be explained by the VTE risk associated with oral contraceptives [57] and pregnancy [58].

Table 1. The annual incidence of VTE by ethnicity, age and gender.

Characteristic	Annual incidence per 1000 individuals
Ethnicity	
White	1.17
Black	0.77–1.41
Asian	0.29
Age (years)	
<15	<0.5
15–44	1.49
45–79	1.92
≥80	5–6
Gender	
Man	1.3
Woman	1.1

VTE: venous thromboembolism;
Table is modified from Beckman et al 2010 [56]

After a VTE event, major bleeding complications [4,59] and other morbidities such as post-thrombotic syndrome, venous insufficiency and chronic pulmonary hypertension, may occur [3]. Moreover, the quality of life after VTE may decline [60]. Nearly 10% of patients are diagnosed with a recurrent VTE [61] and in some studies, as many as a third of all VTE patients encounter a recurrence within ten years after the initial VTE [49,62]. The incidence of recurrent VTE is higher among patients with initially symptomatic PE [63].

VTE causes an economic burden which increases direct healthcare costs. In the United States, healthcare costs of VTE events exceed 7 billion dollars each year [64]. The costs are not only a consequence of the initial hospitalization and treatment of VTE. As many as 5–14% of VTE patients are readmitted to hospital; half of them within three months of the initial diagnosis. [65]

Mortality increases significantly with VTE, especially PE. The highest mortality is seen during the first months after VTE diagnosis. [3,4,49] Patients with symptomatic PE might have an even higher mortality risk than patients with isolated DVT or asymptomatic PE [59]. Worldwide, it has been estimated that one in four deaths is caused by VTE [66,67]. In the European Union countries, VTEs cause around 400 000 deaths a year [47].

2.1.2 General risk factors

VTE is a complex and multifactorial disease involving interactions between acquired and inherited thrombotic risk factors. Some of the variables and clinical factors, that

could predict clot formation and propagation, are defined as predictive risk factors. These factors can guide clinical decision-making for diagnosis and treatment of VTE. There are also risk factors for VTE that can be potentially preventative. Most of the patients with VTE have multiple risk factors [49], but almost one third of VTE events are idiopathic [7,68].

Acquired risk factors can be transient or permanent which has relevance to the duration of anticoagulation. The risk of VTE increases significantly with age [52], and after the age of 40, the risk approximately doubles with each subsequent decade [69]. Other identified risk factors are overweight [70,71], male gender [52], antiphospholipid antibodies [72], microalbuminuria [73], anemia (hemoglobin <12g/dL for women and <13g/dL for men) [74] and other diseases, e.g. inflammatory bowel disease [75], acute bacterial infections [76], thyroid dysfunction [77], HIV-infection [78,79] and dyslipidemia [80]. The most important risk factors are a previous VTE [81] and cancer which increases the risk of VTE seven to nine-fold compared to patients without cancer [26,82–84].

Smoking [85,86], the use of combined oral contraceptives [87,88] or testosterone [89], central venous catheter [84] and long-distance travelling [90] are transient acquired risk factors for VTE. Furthermore, pregnancy and postpartum period [91,92] increase VTE risk 5 to 50-fold. The highest VTE risk is seen among pregnant women with thrombophilia [93]. Physical injuries, e.g. lower extremity fractures and head or spinal injuries, increase VTE risk transiently [94,95]. Surgery is a classical risk factor of VTE [83,95] but the risk varies with the type of surgery. The highest risks are related to major orthopedic or oncological surgeries and coronary artery bypass interventions. In laparoscopic surgery, the risk of VTE is lower than with open surgery. Also, in endoscopy procedures, the VTE risk is minor. [96–98]

A significant part of VTE events occur in outpatients [54,99]. However, a large population-based study showed that nearly every second or third patient with VTE had a history of recent hospitalization [68]. Therefore, the risk of VTE associated with hospitalization seems to continue for one to three months after discharge [84,99], probably due to prolonged immobilization.

2.1.2.1 Inherited thrombophilias

The activation mechanisms of coagulation and fibrinolysis are controlled by various genetic factors [100]. Inherited thrombophilias, such as prothrombin G20210A mutation, factor V Leiden mutation and deficiency of the natural coagulant inhibitors (e.g. protein C, protein S and antithrombin), lead to hypercoagulation and increased VTE risk. Factors inhibiting fibrinolysis (hypofibrinolysis), such as plasminogen activator inhibitor type 1, have been also associated with increased risk of VTE. [101–105]

2.1.3 Pathogenesis

Simply put, thrombosis means a blood clot formed in a vein which may develop into an obstructing thrombus preventing blood flow through the circulatory system. If the thrombus, or part of it, migrates into the circulatory system, it may block an artery or a vein, causing an embolism. Thrombosis is a result of imbalance of a complex homeostasis between blood cells (e.g. platelets, red blood cells), plasma proteins, coagulation factors, inflammatory factors, cytokines and endothelial surface of the veins. The most well-known theory of thrombosis is the Virchow's triad where three factors predispose to VTE: hypercoagulability of blood, variation in blood flow in the vein, and damage / injury to the endothelial vessel wall [1]. Historically, the formation of venous thrombosis has been considered with reference to the Virchow's triad [106]. It is still one of the basic medical principles by which some of the risk factors for VTE are still categorized over 160 years later.

2.1.3.1 Normal hemostasis

To understand abnormalities of the prothrombic and hypercoagulable states (also known as thrombophilia) in the process of thrombosis, it is important to acknowledge normal hemostasis. Damage to a blood vessel leads to its' vasoconstriction. At the same time, collagen/extracellular matrix from the disrupted endothelial lining is exposed to blood components. The releasing cytokines and inflammatory factors allow platelets to adhere, activate and aggregate to form a platelet plug of the damaged area. [107] The actual mechanism of the coagulation process is more complex and multifactorial. While coagulation factors are increased, several inhibitors control clot formation and restrict thrombus propagation elsewhere in the circulatory system. [108]

Traditionally, the coagulation cascade is triggered by two distinct pathways (**Figure 1**): the intrinsic pathway (i.e. contact pathway) and the extrinsic pathway (i.e. tissue factor (TF) pathway) which both converge on factor X [107–109]. TF is a transmembrane receptor on the cell surface (i.e. tissue thromboplastin or factor III) mainly in the cells located in medial layers of the vascular wall [110]. When cells expressing TF are exposed to blood, the TF pathway is triggered: cell-surface complex of TF interacts with factor VII and activates it (factor VIIa). Furthermore, the factor VIIa activates factor IX and factor X by proteolysis. The activated factor IX (factor IXa) adheres to its cofactor and activates factor VIII which leads to activation of factor X (factor Xa) that binds to activated factor V (factor Va) and to calcium. From this cascade, a prothrombinase-complex develops and transforms prothrombin into thrombin. On the other hand, the intrinsic pathway is triggered when factor XII contacts the negative charges of endothelium and is activated by clotting factors. The activated factor XII (factor XIIa) further activates the factor XI. The activated factor XI (factor XIa) activates the factor IX and the activated factor

IX (factor IXa) adheres to its cofactor and forms a complex which activates factor X. Finally, thrombin transforms into fibrinogen and releases fibrin into the plasma, resulting in platelet activation and clot formation. [108,109]

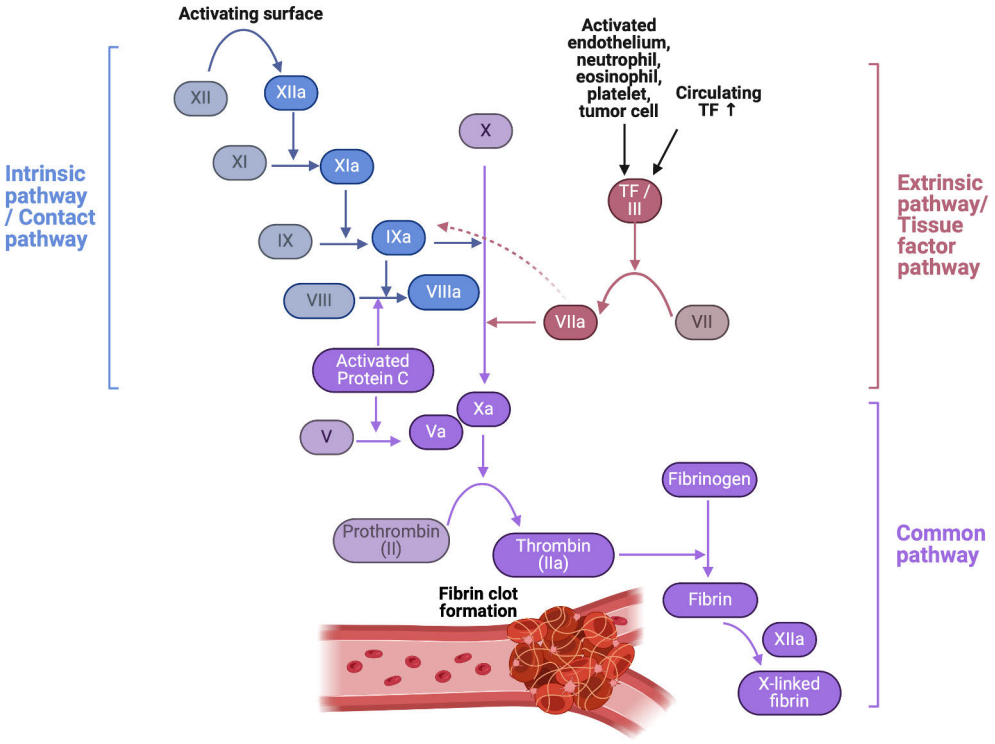

Figure 1. Normal hemostasis and thrombosis. The coagulation cascade is triggered by two distinct pathways: the intrinsic pathway and the extrinsic pathway (also known as the TF pathway). Both pathways lead to factor X activation and the common pathway, where prothrombin is activated into active enzyme thrombin that cleaves fibrinogen and turns it into fibrin. The intrinsic pathway starts from the activation of factor XII by contact with the activating surface of endothelium. Factor XIIa further activates factor XI: factor XIa activates factor IX: factor IXa adheres to its cofactor and forms a complex which activates factor X. In the TF pathway, factor VII is activated (VIIa) by the interaction with TF on the surface of activated endothelium, neutrophil, eosinophil, platelet or tumor cells. TF: tissue factor. Figure 1 was created with BioRender.com.

2.1.3.2 Pathophysiology

Prothrombic and hypercoagulable states are a continuum of normal hemostasis, but when the process is triggered inappropriately, it leads to thrombosis. As simplified, VTE is a consequence of imbalance between the procoagulant activity and inhibitors: the coagulation factors may be increased, or the activity of naturally occurring inhibitors may be decreased. So, the theory of the Virchow's triad is controversial as

the combination of stasis and hypercoagulation could be more crucial for the development of VTE than endothelial damage. [111]

The exact mechanisms of the pathogenesis of VTE are not quite understood, but certain coagulation factors (e.g. factor VIII and factor VII) increase significantly with age and may predispose to thrombotic conditions [112]. Immobility reduces blood flow in the venous system, especially in the venous valves, which can lead to hypercoagulability [113] and eventually the development of thrombus.

The TF pathway triggers blood clotting in many types of thrombosis **Figure 1**. The inflammatory mediators increase the occurrence of TF on cell surfaces of the vascular wall [114]. On the other hand, TF is also abnormally expressed on blood cells (such as neutrophils, eosinophils and platelets) surfaces during in infection and in cardiovascular diseases [115–118]. There are normally low levels of TF in the blood (known as circulating TF), mostly present in the form of microparticles. TF levels increase during surgery and trauma [111] as well as in various diseases, including cardiovascular disease, sepsis, diabetes, and cancer, which may cause inappropriate thrombus formation [116,119].

Inherited deficiency of anticoagulation factors like protein C, protein S and antithrombin, can be linked to the development of VTE [101–104]. The deficiency of protein C causes inactivation of factor Va and factor VIIIa decreases. Therefore, the fibrinolytic capacity of blood is reduced, and the formation of fibrin increases leading to thrombosis. [101] The deficiency of antithrombin reduces the inhibition of thrombin and factor Xa which increases clot formation and may cause thrombosis [104].

2.2 Cancer and VTE

2.2.1 Epidemiology

Twenty percent of all new VTE cases are associated with an existing malignancy and, within one year, 5% of VTE patients are diagnosed with cancer [7–10]. Although VTE can be the first symptom of a presenting malignancy, more often it is a manifestation of the advanced stage of cancer [120]. Approximately 4–6 % of cancer-associated VTEs are incidental and asymptomatic [121,122]. Moreover, the incidence of VTE in cancer patients has increased during the last decade, and the risk of VTE is now 7–9-fold higher in cancer patients than in the general population. This may be due to many reasons, such as the patients' longer survival, anticancer therapies and the increased diagnosis of incidental VTEs. [26,123]

VTE in cancer patients is common and the incidence is 0.5% to 20% or approximately 14 per 1000 person years including all cancer patients [13,25,26,124–126]. The incidence of VTE depends on the type of cancer as shown in **Table 2**.

Table 2. The incidence of VTE in various cancers (excluding hematologic malignancies).

Study	**Mahajan et al. 2022**	**Mulder et al. 2021**	**Walker et al. 2013**	**Stein et al. 2006**	**Blom et al. 2006**	**Chew et al. 2006**	**Levitan et al.1999**
Study design	Cohort study of California Cancer Registry, California Patient Discharge Database and the Emergency Department Utilization Database	Cohort study of Danish national medical registries	Cohort study of Clinical Practice Research datalink	Cohort study of National Hospital Discharge Survey database	Cohort study of Cancer Registry and anti-coagulant database	Cohort study of California Cancer registry linked to Discharge Data	Cohort study of Medicare Discharge data
Overall patients	942 019	499 092	83 203	827 000	66 329	235 149	46 848
	Cumulative incidence, 12 months overall	Rate per 100 person years 6 months after cancer diagnosis	Rate per 100 person years	Rate per 100 hospitali-zation	Cumula-tive per 100 patients	First year rate of VTE / patient-years, remote disease	Rate per 100 hospitali-zation
Site of cancer							
Bladder	5.1%	3.8%	1.5%	1.0%	1.3%	7.9%	0.2%
Brain	9.7%	5.5%	4.0%	3.5%	3.2%	*NR*	1.2%
Breast	1.0%	1.3%	0.9%	1.7%	0.8%	2.8%	0.2%
Colon	3.9% *	5.1%	*NR*	1.9%	1.3%	4.3% *	0.8%
Esophagus	*NR*	5.8%	3.7%	2.0%	1.3%	*NR*	0.4%
Kidney	3.6%	5.1%	1.3%	2.0%	1.3%	6.0%	0.8%
Liver	NR	10.4%	3.5%	1.8% **	0.7%	*NR*	0.7%
Lung	6.8%	7.4%	4.4%	2.1%	1.4%	5.0%	0.6%
Ovary	8.2%	7.2%	3.1%	1.9%	3.6%	3.6%	1.2%
Pancreas	10.8%	15.6%	9.8%	4.3%	2.3%	20.0%	1.1%
Prostatae	1.0%	1.7%	0.9%	2.0%	1.0%	0.9%	0.6%
Stomach	6.7%	6.6%	3.7%	2.7%	1.5%	10.7%	0.9%
Testicular	*NR*	1.6%	0.3%	*NR*	*NR*	*NR*	1.0%

NR: Not reported

* including rectal cancer

** including gallbladder cancers, intra- and extraductal hepatobiliary cancers

The incidence of VTE can be affected by the patient's age and comorbidities, VTE's proximity to cancer diagnosis, as well as the stage and treatment strategy of cancer [27,127–129]. The highest VTE incidence rates are reported in the first 3–12 months after cancer diagnosis and during chemotherapy [13,27,130], especially during cisplatin-based chemotherapy [131]. Also, novel cancer treatments, like immune checkpoint inhibitors [132,133] and cyclin dependent kinase 4/6 inhibitors [134] may be related to the increased incidence of VTE.

VTE in cancer patients leads often to hospitalization. VTE may delay or interrupt systemic anticancer therapies and add the patients' distress [14,15]. It also increases morbidity with a very high risk of a recurrent VTE and bleeding complications related to anticoagulant treatment [67,135–138]. The medical costs are over 2-fold higher for cancer patients with VTE compared to controls, and the costs may continue to increase for years [139].

VTE is the most common cause of death in cancer patients after the cancer itself [18] and it is also a predictive factor of death [140,141]. The mortality rate is 2–3-fold higher in cancer patients with VTE than those without a VTE [10,25,26,136].

2.2.2 Risk factors

Similar to the general population, VTE in cancer patients is a multifactorial disease and the risk factors can be categorized into patient- and cancer-related, see **Table 3**. The clinical risk factors are often combined and synergistic, and cannot be influenced, except for a few treatment options for cancer.

Table 3 The risk factors for cancer-associated thrombosis.

	Increases the risk of VTE	Possibly increases the risk of VTE
Patient-related factors		
Comorbidities (e.g. obesity, diabetes, dyslipidemia, hypertension)	x	
Advanced age		x
Prior history of VTE	x	
Cancer-related factors		
Primary site of cancer (e.g. pancreas, stomach, brain, ovary and lung)	x	
Advanced stage of cancer	x	
Histology (e.g. adenocarcinoma)	x	
Cancer treatment-related factors		
Cancer surgery	x	
Radiotherapy		x
Chemotherapy	x	
Cisplatin	x	
Carboplatin	x	
Oxaliplatin		x
Anthracycline	x	
Anti-angiogenic agents (e.g. bevacizumab)	x	
Immune checkpoint inhibitors		x
Hormonal therapy		
Tamoxifen	x	
Cyclin dependent kinase 4/6 inhibitors	x	
Supportive therapy		
Blood transfusions	x	
Erythropoiesis stimulating agents	x	
Granulocyte colony stimulating factors	x	
Central venous catheter	x	
Hospitalization	x	

VTE: venous thromboembolism

2.2.2.1 Individual characteristics

The risk of VTE in cancer patients increases with the presence of comorbidities like obesity, hypertension, dyslipidemia, stroke and diabetes [17,25,71,130,142]. Sepsis and pneumonia are also strong individual risk factors for VTE [17]. Gender and age are not as significant risk factors for VTE among cancer patients than in the general population. However, advanced age is a modest risk factor because it has effects on survival after VTE [126,143]. Also, same hereditary factors (e.g. factor V Leiden and

prothrombin 20210A mutations) than in the general population increase the risk of VTE among cancer patients [82,144].

2.2.2.2 Cancer-related risk factors

The most important risk factors for VTE are both the stage and type of cancer. Adenocarcinomas [27], high-grade tumors [145] and tumors of the intra-abdominal or pelvic organs [146] are associated with high risk of VTE. More specifically, pancreatic, gastric and ovarian cancer are the cancer types with the highest risk of VTE but also brain tumors (e,g, glioblastoma), kidney and lung cancers are associated with a high VTE risk. The VTE risk is highest during the first three to six months after cancer diagnosis but the risk is elevated already six months prior to cancer diagnosis. Advanced disease, particularly distant metastasis, is an independent risk factor for VTE and the risk of VTE can be 2 to 20-fold compared with local disease. [12,26,27,123,126,141,144,149,150]

2.2.2.3 Associated cancer treatments

Cancer patients have a significantly higher risk of post-operative VTE than patients without malignant diseases [147], and cancer surgery is a considerable risk factor of VTE [11,148]. Radiotherapy may also be associated with an increased risk of VTE [149] but controversial results have been reported [13,150].

Chemotherapy is a well-documented risk factor with a two- to six-fold higher risk of VTE depending on the anticancer medicine used [12,13,26,71,143] . In particular, cisplatin- and carboplatin-based regimens are associated with a high VTE risk [131,151–153]. The role of oxaliplatin as a potential risk factor is unclear [154]. Also, a few other anticancer treatments, e.g. bevacizumab (monoclonal antibody of vascular endothelial growth factor) [26,155], estrogen receptor modulator tamoxifen [156] and cyclin dependent kinase 4/6 inhibitors increase the risk of VTE [157]. Immune checkpoint inhibitors may also increase the incidence of VTE [132,133], but their role is still under research [158]. The response to systemic anticancer treatment influences VTE risk while patients with partial remission or no response have a higher risk compared to patients in complete remission [71].

The use of supportive therapies during cancer treatment, e.g. erythropoiesis stimulating agents (ESAs) and granulocyte colony stimulating factors (G-CSFs), is associated with an increased risk of VTE [131,143,159,160]. However, blood transfusions might confer a higher VTE risk than ESAs in the treatment of cancer-related anemia [161]. The presence of a central venous catheter is also a well-documented independent risk factor for VTE in cancer patients [162].

2.2.2.4 Laboratory parameters

High platelet counts prior to cancer diagnosis [163], at the time of cancer diagnosis and before chemotherapy [71,164,165] are associated with increased risk of VTE. Also, leukocytosis and anemia prior to cancer diagnosis and before chemotherapy increase the risk of VTE [24,166]. Increased levels of soluble P-selectin [167], a short activated partial thromboplastin time (aPTT) [168] as well as elevated levels of D-dimer, prothrombin fragment 1+2 [169] and factor VIII [170] are all described as risk factors for VTE in cancer patients.

2.2.3 Pathogenesis

While the association between cancer and venous thrombosis has been known for over a century, it is still unclear how malignancy affects the hemostatic system, and whether a thromboembolic event can be predicted. A French physician Armand Trousseau (1801–1867) described the relationship between venous thrombosis and cancer in 1865. This discovery later came to be known as Trousseau's syndrome which referred to migratory thrombophlebitis as a sign of visceral malignancy. [171] An analysis by Sack and the colleagues in 1977 extended this description to involve chronic disseminated intravascular coagulopathy associated with microangiopathy, and arterial emboli in patients with mucin-positive carcinomas [172]. While many coagulation abnormalities have been reported in cancer patients (**Figure 2**), the exact mechanisms of thrombosis in malignancy remain ambiguous.

Malignant cells may promote fibrin formation in the tumor microenvironment [173] and release soluble procoagulant molecules, such as cancer procoagulant, which may affect the clotting cascade [174]. Cancer procoagulant is produced by malignant cells and activates factor X directly without factor VIIa [175,176]. For decades, it has been recognized that different cancer cells express TF on the surface of the cell membrane [173], increase the levels of circulating TF into the forms of microparticles [177] and induce the expression of TF on other cells' surface, such as endothelial cells and monocytes [178], which can all trigger blood coagulation. Cancer cells can also activate the plasminogen activator inhibitors directly which may increase the probability of VTE development [175]. The 21st century studies have shown that cancer cells can stimulate neutrophils, and upon their activation, neutrophils release extracellular chromatin in a process that leads to the generation of neutrophil extracellular traps (NETs). These NETs have a role in the process of venous thrombosis formation and therefore, they likely contribute to VTE risk. [179,180] Also, inflammatory cytokines, such as a tumor necrosis factor [181], interleukin-1 [182] and vascular endothelial growth factor (VEGF) [183], are produced by cancer cells which cause procoagulant activity.

Cancer treatments also cause coagulation abnormalities, although the mechanisms are not totally understood. Chemotherapy can damage the endothelial cells [184] which will decrease plasma anticoagulant proteins, such as protein C and protein S, [185] and increase procoagulants, such as TF [186], leading to the activation of coagulation (**Figure 2**). Injured endothelial cells can release prostacyclin and thromboxane that increase platelet adhesion and aggregation, predisposing to thrombosis [176]. On the other hand, anticancer treatments can also directly activate platelets [186]. Moreover, patients' characteristics (e.g. gender, previous VTE, body mass index (BMI)) and comorbidities can impact the mechanisms of hypercoagulability in cancer patients [187].

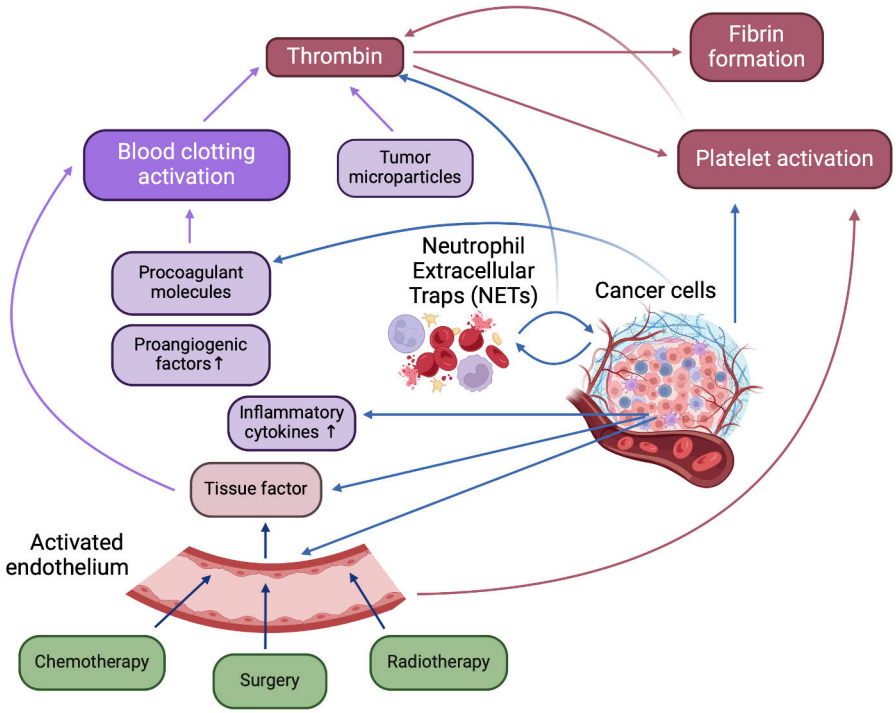

Figure 2. Cancer cells may release inflammatory cytokines and soluble procoagulant molecules that cause procoagulant activity. Also, cancer cells express TF, increase the levels of circulating TF in the form of microparticles and induce the expression of TF on other cell surfaces, such as endothelium. Interactions between immune and cancer cells produce procoagulant activity by many mechanisms. For example, neutrophils can release neutrophil extracellular traps (NETs) which have prothrombotic and platelet-activating properties. Chemotherapy, radiotherapy and surgery can damage the endothelium as a result of inflammatory cytokines and procoagulants are released to activate coagulation. Also, injured endothelial cells and anticancer treatments can directly activate platelets. TF: tissue factor; NETs: neutrophil extracellular traps (NETs). The Figure was created with BioRender.com

2.3 Clinical features of pancreatic cancer

2.3.1 Epidemiology

Pancreatic cancer is the 14th most common cancer worldwide with the annual incidence of almost half a million [188,189]. The highest incidence rates are in high-income countries [190,191] where the incidence has more than doubled during the past decades [189]. The incidence is slightly higher among men than women [189,192]. According to Finnish Cancer registry data, in 2020 PC was diagnosed in 1193 people of whom 596 were male and 597 female [193].

Histologically, there are two subtypes of PC. Ductal adenocarcinoma is the most common subtype (about 90–95%), while cancers with neuroendocrine differentiation are rare (5%). These tumors differ markedly in biological features, morphology and prognosis, and they are treated with different approaches. [194 195] In this thesis, the term PC explicitly refers to ductal adenocarcinoma of the pancreas.

The median age at diagnosis of PC is 70–74 years and only 10% of the patients are under the age of 50 years [192]. Age is one of the major risk factors of PC [196]. The risk of PC also increases with smoking [197,198] as well as obesity [199], diabetes mellitus [200], low physical activity [201], excessive alcohol use and chronic pancreatitis [192,196]. Less than 10% of all PCs are caused by inherited factors, with several inherited germ line mutations. The most common is the breast cancer (BRCA) gene 2 mutation which can lead to a four-fold increase in the risk of PC [202–204], and the BRCA gene 1 mutation carriers also have a moderate risk [205]. Furthermore, Lynch syndrome is associated with an increased risk of PC; the risk is almost nine-fold higher compared to the general population [206].

PC is frequently diagnosed as a metastatic or locally advanced disease and not eligible for curative surgery. Only approximately 5–10% of patients with advanced stage PC are still alive within five years of diagnosis. [207,208] PC is the 7th most common cause of cancer death worldwide [191] with over 460 000 deaths each year [188]. In Finland, PC caused 1 392 deaths in 2020 [193]. In developed countries, PC is the fourth or fifth leading cause of cancer mortality [209,210].

2.3.2 Diagnostics and treatment

The symptoms of PC are usually non-specific and appear late when the cancer has already disseminated. The signs include fatigue, weight loss, nausea, obstructive jaundice, abdominal pain (which typically radiates to the back), and sometimes newly diagnosed diabetes mellitus. [211,212]

Combinations of different imaging modalities are used to diagnose PC, but the triphasic pancreatic/tumor protocol computed tomography (CT) is the standard and

best validated tool for diagnosis and staging. Magnetic resonance imaging (MRI) can be used as an additional diagnostic modality. A cytologic sample is recommended to confirm the cancer diagnosis and to define the histologic type. The sample can be taken via an endoscopic/endoluminal ultrasound (EUS) or CT-guided fine-needle aspiration. Alternatively, brushings for cytological sample can be acquired during endoscopic retrograde cholangiopancreatography (ERCP). [211,212]

The only serum biomarker for the diagnosis of PC in symptomatic patients is serum carbohydrate antigen 19-9 (CA 19-9) [213] , also known as monosialylated Lewis or Sialyl-Lewis-A [214]. CA 19-9 is a cell surface glycoprotein complex that was first defined in colorectal cancer [215] . The expression of CA 19-9 requires the Lewis gene product. In PC, CA 19-9 is also associated with prognosis, overall survival (OS), and response to chemotherapy. CA 19-9 values are routinely followed during the course of disease and rising values indicate post-operative recurrence. [216,217]

The marker CA 19-9 is not specific for PC, since elevated values are associated also with biliary tract cancer [218], colorectal and gastric cancer [219]. Furthermore, in non-malignant disorders, like acute pancreatitis due to a gallstone, [220] biliary obstruction and cholangitis [221], serum CA 19-9 values can be elevated. The presence of jaundice increases the level of CA 19-9 and therefore elevated values should be verified after the relief of jaundice [213]. Also, some people lack the functional Lewis enzyme that contributes to CA 19-9 synthesis. Consequently, the serum levels of CA 19-9 are usually not detectable or stay below 1.0 U/ml in disorders where they typically would increase. [222,223]

For all patients with localized PC, the multidisciplinary tumor board gives a recommendation of treatment practice on a case-by-case basis [224]. Approximately <20% of patients with PC have a surgically resectable disease at the time of cancer diagnosis [225]. The potentially curative treatment always consists of surgery (pancreatico-duodenectomy, i.e. Whipple's procedure) and pre- or/and post-operative system chemotherapy for three to six months. The pre- and post-operative chemotherapy is a combination of 5-fluorouracil with folinic acid, irinotecan and oxaliplatin (i.e. FOLFIRINOX) for patients with good performance status. For more fragile patients, chemotherapy is provided as single-agent gemcitabine or gemcitabine combined with nanoparticle-formulated paclitaxel preoperatively and with 5-fluorouracil postoperatively. Chemoradiotherapy or radiotherapy may be considered in certain circumstances.

Treatment of metastatic PC is based on the chemotherapy substances described above and it should also include palliative symptom control. The poly (ADP-ribose) polymerase (PARP) inhibitors have been studied in patients with germline BRCA mutation-related PC, and e.g. olaparib should be considered as maintenance treatment after platinum-based chemotherapy. PC is not considered an immunogenic

cancer and so far, immunotherapy (immune checkpoint inhibitors) is not recommended as part of standard care. [194,196,212,224,226]

2.3.3 VTE in pancreatic cancer

Patients with PC present one of the highest incidences of VTE and the rate of VTE varies widely from 4% to over 40% [13,25,34,123,126,227]. It is roughly estimated that over one fourth or even one third of patients with PC develop VTE during the course of the disease [35].

Patients with a primary tumor of the corpus or caudal region of pancreas have a 2-fold increased risk for VTE compared to patients with tumors of the caput [228]. The risk of VTE is also higher among PC patients with comorbidities or with metastatic disease, during chemotherapy [227–229] or ESA use [230]. However, chemotherapy regimens (gemcitabine-based versus intensive FOLFIRINOX) do not appear to affect the risk of VTE [231]. PC patients have a 4.5-fold increased risk of VTE after 30 days of surgery [228] and the risk remains high for up to 90 days [232].

Based on a recent study, coagulation biomarkers, e.g. fibrinogen and FVIII, can improve the diagnostic accuracy of PC [233]. These results confirm that PC is strongly associated with the hypercoagulable state. PC cells can activate platelets and express several procoagulant factors, including TF and thrombin [234]. Pancreatic malignant tumors contain the highest levels of TF and release TF in the form of microparticles to the circulation which in turn activates the clotting system and increases VTE events. TF expression is also associated with the expression of VEGF, and therefore the activation of coagulation not only affects thrombosis, but it might also be linked to enhanced tumor growth and angiogenesis. [24,29,32,33,235,236]

VTE, both symptomatic and incidental, increases mortality among patients with PC [34,35]. The highest risk of death is when the VTE is diagnosed less than two or three months after cancer diagnosis [230,232]. Also, VTE that emerges shortly after PC diagnosis is associated with a poor prognosis of PC [227].

2.4 Clinical features of epithelial ovarian cancer

2.4.1 Epidemiology

Ovarian cancer (OC) is globally the 7th most common cancer among women and the third most common gynecologic cancer, with over 300 000 annual diagnoses worldwide [188]. In Finland, 563 new OC cases were diagnosed in 2020 [193]. Histologically, OC can be divided into epithelial cancers (representing 90% of cases) and non-epithelial cancers. Epithelial ovarian cancer (EOC) is divided into different histopathological subtypes, including high-grade serous (HGSOC) (70%),

endometrioid (10%), clear cell (6–10%), low-grade serous (< 5%) and mucinous EOC (3–4%). [237,238] The various EOC subtypes differ in their molecular characteristics and outcome, with HGSOC being the most aggressive.

The median age at EOC diagnosis is 55–79 years and therefore, EOC is mainly a disease of postmenopausal women [239–241]. Various genetic, environmental and lifestyle factors are associated with EOC but their role as risk factors vary between different subtypes. Infertility treatments, the use of menopausal hormone therapy and smoking potentially increase the risk of particularly serous cancer type. [242,243] Hereditary EOC, especially HGSOC, is mostly associated with germline mutations in BRCA1 or BRCA2, with a smaller proportion linked to Lynch syndrome or other genes [244,245].

EOC is often diagnosed as a metastatic or locally advanced disease (stage III-IV) and therefore, the prognosis is poor: less than 30% of patients are still alive after five years of diagnosis [239,246]. Also, HGSOCs are diagnosed at stage III in half of all cases and almost a third are stage IV, with a 5-year OS less than 50% [247]. Overall, OC is the second most lethal gynecologic cancer in high-income countries, causing over 200 000 deaths per year [188] with 70–80% accounted for by HGSOC [248].

2.4.2 Diagnostics and treatment

Since HGSOC is the most common histologic type of EOC, in practice EOC diagnostics and treatment mainly refers to HGSOC. EOC may be asymptomatic or mildly symptomatic in the early stages. In the advanced disease, the symptoms are usually non-specific, like unusual bloating, fullness and pressure, abdominal or back pain, urgent or frequent urination, appetite loss or early satiety, and fatigue. [249–251] Palpation of the abdomen with a pelvic mass, ascites or abdominal distension may be suggestive of EOC [252]. Transvaginal ultrasonography is the primary imaging modality for the diagnosis of malignant lesions of ovaries [250,253].

The standard of laboratory testing for EOC is cancer antigen 12-5 (CA 12-5) which is a high molecular weight glycoprotein overexpressed in the cells of EOC and secreted into the blood [254,255]. The plasma level of CA 12-5 has a low specificity for EOC since it varies for many other reasons, e.g. age, obesity, the presence of endometriosis, a history of hysterectomy, current hormone therapy use, and other malignancies such as breast cancer [256–258]. Additionally, the marker CA 12-5 has a low sensitivity in the early stages of EOC [259]. The human epididymis protein 4 (HE4) is also overexpressed in EOC [260]. The combination of HE4 and CA 12-5 might be the most efficient biomarker for diagnosing EOC [261], and different algorithms based on them have been developed (e.g. Risk Malignancy Index, The risk of ovarian malignancy algorithm) [262].

After preliminary assessments suggestive of EOC, further imaging continues with CT of the abdomen, pelvis and thorax and/or MRI of the pelvis [263–265]. This is usually followed by a staging procedure to explore the peritoneal cavity, assess the extent of the disease and take biopsies for histologic confirmation and somatic testing [266].

The multidisciplinary team provides a recommendation of the treatment practice on a case-by-case basis. The recommendation is to use a multimodality approach in the treatment of advanced ovarian cancer, including aggressive and radical cytoreductive surgery to remove as much of the visible tumor as possible, and combination chemotherapy. Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is an alternative to upfront primary debulking surgery (PDS) followed by adjuvant chemotherapy. [266–268]

A platinum- and taxane- based doublet is the standard for NACT and adjuvant therapy, but alternative regimens, e.g. bevacizumab, olaparib and niraparib, can be selected in addition, on a case-by-case basis considering individual factors (e.g. genetic mutations). [266–268] Response to second-line platinum is less likely if there is a short time between the last dose of platinum-based chemotherapy and recurrence [269].The second-line treatment is dependent on whether EOC is resistant or sensitive to platinum, based on the platinum-free-interval (PFI). Platinum-based chemotherapy combined with bevacizumab and/or olaparib or niraparib (if BRCA mutation present) is recommended in platinum sensitive disease. Non-platinum-based chemotherapy can include topotecan, taxane-based regimens, gemcitabine and liposomal doxorubicin. [268,270–272]

2.4.3 VTE in ovarian cancer

OC has one of the highest incidences of cancer-related VTE [125]. In general, the incidence of VTE in patients with OC varies from 1% to 10% [13,25–27,123,126]. In studies that have focused on VTE among OC patients only, the VTE incidence is usually 5–25%, and in local OC 1–2% [38,39,273–277]. The highest proportion of VTEs is associated with EOC but it remains controversial whether the highest incidence is related to clear cell cancer [278–282] or HGSOC [273,283].

The highest VTE incidence is seen during the first three months after OC diagnosis and it decreases over time [39]. However, a few prospective studies have reported that a significant proportion of VTEs are asymptomatic (25–84%) prior to the initiation of cancer treatments [279]. Chemotherapy, advancing age, comorbidities, BMI, advanced state or residual disease, invasive histology, ascites and surgery are significant high-risk factors for VTE in patients with OC [38,39,274,281]. Also, transfusion during surgery [285] and the use of bevacizumab anticancer treatment increase the risk of VTE among OC patients [284–286].

The exact biological mechanism of hypercoagulation in OC is still under research, but OC cells, like HGSOC, express TF [28] and microparticles with TF-factor VIIa activity [30,31] that can cause thrombosis in the same way as in PC cells.

Patients with VTE have a poorer prognosis of OC than patients without VTE and also a higher mortality [38–40].

2.4.3.1 VTE in epithelial ovarian cancer

Most studies of VTE and OC have used large register data where the histological subtypes have not been distinguished. There are only few studies that have focused specifically on the prevalence and risk factors of VTE in EOC patients.

Among women with advanced EOC, the incidence of VTE is high, up to 20% [287–290]. Probably the incidence is even higher considering the asymptomatic VTEs [280] which may be unobserved. The highest risk of VTE in patients with EOC is within one to two months after primary radical surgery without the appropriate prophylaxis regimens [37,288].

Surgery is one of the major risk factors for VTE [291] and especially surgery with NACT as a primary cancer treatment [292]. A fourth of EOC patients undergoing NACT develop VTE during chemotherapy [277] with nearly half of those diagnosed before interval debulking surgery [273]. Also, chemotherapy alone is a significant risk factor [289,292], as well as BMI over 30kg /m^2, smoking, advanced age, multiple comorbid conditions, advanced stage of cancer and ascites [37,287,289,291]. VTE reduces survival of the patients at all stages of EOC [37].

2.5 Diagnostics of VTE

2.5.1 Diagnostics of VTE in general population

A strong clinical probability of VTE guides the diagnostic tests. DVT should be suspected in any patient with unexplained symptoms of swelling, pain, warmth or erythema in an extremity. The clinical signs and symptoms of acute PE are more non-specific. In most cases, PE can cause dyspnea, chest or back pain, but also syncope or hemoptysis and sometimes even sudden death. As these symptoms may also be due to many other diseases, the probability of VTE should be estimated by a combination of symptoms and clinical findings, including the presence of risk factors for VTE. [293–296] This assessment of clinical probability allows the classification of patients with suspected VTE into distinct clinical categories: low, intermediate/moderate and high probability of VTE (**Table 4**) [297–299].

Table 4. The clinical prediction for VTE. Modified from the Wells rule [a] (score for DVT of lower limb) and the revised Geneva rule [b] (score for PE).

Clinical characteristic	Score for DVT [a]	Score for PE [b]
Previous DVT or PE	1	1
Heart rate		
75–94 bpm	*NA*	1
≥95 bpm	*NA*	2
Bedridden for ≥ 3 days or major surgery within past 3 months requiring general or regional anesthesia	1	*NA*
Surgery or fracture within the past month	*NA*	1
Hemoptysis	*NA*	1
Active cancer	1	1
Unilateral limb pain	*NA*	1
Pain on lower-limb deep venous palpation and unilateral oedema	1	1
Swelling ≥3cm larger than on the asymptomatic side	1	*NA*
Entire leg swelling	1	*NA*

VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; bpm: beats per minute; NA: Not assessed

[a] Modified from the Wells rule from Silveira et al. 2015 [298]

[b] Modified from revised Geneva rule from Klok et al. 2008 [299]

If the clinical probability of VTE remains uncertain, plasma D-dimer testing can be used with certain restrictions. D-dimer is the plasmin degradation product of fibrin. Its' levels are increased in plasma during acute thrombosis because coagulation and fibrinolysis are both activated at the same time. [300] The negative predictive value of D-dimer testing is high because a normal D-dimer very likely excludes PE. Therefore, it can be used for patients with unlikely or low probability for PE or DVT. [294–296,301] However, elevated D-dimer levels cannot be used for the diagnosis of PE as testing can only be used to exclude PE [302]. The use of D-dimer is also limited by the fact that many factors elevate D-dimer levels, including cancer [303,304], hospitalization [305], infection, coronavirus disease 2019 (COVID-19) [306], inflammatory diseases and pregnancy [307].

VTE diagnosis is always based on imaging. Venous compression ultrasound is the standard imaging modality for DVT [294–296,301], although its' use is limited to examination of the proximal veins, e.g. the common femoral and popliteal veins [308]. Patients with clinically diagnosed DVT and without symptoms of PE may still have radiological evidence of PE [309,310] but routinely there is no need to exclude PE radiologically [295,296,301]. For the diagnosis of PE, computed tomography pulmonary angiography is regarded as the gold standard, with ventilation-perfusion lung scanning imaging as an alternative [294,296,301]. These diagnostic procedures are

recommended also in the updated Finnish national guideline of the diagnosis and treatment of DVT and PE [293].

2.5.2 Diagnostics of VTE in cancer patients

The symptoms and clinical findings of VTE in cancer patients are not specific and therefore imaging is always necessary to confirm the diagnosis: venous compression ultrasound for DVT and computed tomography pulmonary angiography for PE [311]. The same clinical probability assessment for VTE that is used in the general population can be used in cancer patients (see **Table 4**) although the predictive value is weak [312]. D-dimer testing is not recommended in cancer patients [311] although a normal D-dimer value also excludes the diagnosis of PE in cancer patients [304]. Cancer often increases the D-dimer levels [303] without PE and therefore D-dimer level is rarely normal in cancer patients. Incidental VTEs are commonly diagnosed during frequent imaging tests for cancer diagnosis, staging, and follow-up without clinically relevant symptoms [121].

2.6 Treatment of VTE

2.6.1 Treatment of VTE in general population

The treatment of VTE is based on medications with different mechanisms affecting the blood clotting cascade. Low-molecular weight heparin (LMWH) activates antithrombin which accelerates the inactivation of coagulation enzymes, factor Xa and factor IXa. LMWH is dosed subcutaneously (s.c) once or twice per day depending on the active substance and on various characteristics of the patient. [313,314] Fondaparinux, an inhibitor of factor Xa is used s.c. and dosed once per day [315].

Direct oral anticoagulants (DOACs) are small molecules that directly inhibit either thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban and edoxaban) [316]. There are also parenteral direct thrombin inhbitors, such as argatroban and bivalirudin for use in special clinical settings [317].

Until recent years, vitamin K antagonists (VKAs), i.e. warfarin, were standard oral anticoagulation treatment. However, the current recommendation is to primarily use DOACs. LMWH should be considered for selected subgroups of patients with elevated bleeding risks, e.g. those with renal or liver insufficiency, thrombocytopenia (platelet count below 100×10^9/L) or anemia (hemoglobin level below 100 g/dL). [294–296,318]

Most patients with DVT and several patients with PE can be treated as outpatients, if appropriate risk assessment has been completed [294–296,318]. Patients

with proximal DVT should use an elastic compression textile and do walking exercise to avoid immobilization [319].

As an alternative treatment, thrombolysis can be considered in certain situations, such as limb-threatening DVT (catheter-directed thrombolysis) or submassive PE (systemic thrombolysis). Also, insertion of an inferior vena cava filter can be used if anticoagulation is contraindicated in patients with proximal DVT. Surgical pulmonary embolectomy is rarely required but may be considered if thrombolysis is contraindicated or has failed in patients with massive PE. [294–296,318]

Therapy for VTE can be divided into the acute or initial phase, covering the first days after diagnosis and followed by a treatment period, and the next three to six months (primary treatment). After that, extended treatment is based upon the risk of VTE recurrence (secondary prevention). In general, primary treatment of the initial VTE can be stopped after three to six months if the provoked temporary risk factors for the initial VTE are gone. With a recurrent VTE, or if the initial VTE was unprovoked or provoked by a chronic risk factor, anticoagulant therapy is recommended to continue as extended primary treatment up to six to twelve months and/or after secondary prevention indefinitely. The decision to continue or discontinue anticoagulation should always be made on an individual basis, balancing the risks of bleeding and of recurrence, and considering the patients' preferences, and reassessing the decision regularly. [293–296,318]

2.6.2 Treatment of VTE in cancer patients

Cancer patients often suffer from multiple comorbidities [25,187] and are at a high risk for bleeding complications. The risk of bleeding varies according to type of cancer [20,67] and ongoing chemotherapy [320]. Therefore, choosing the anticoagulation treatment of VTE is challenging. Careful assessment of comorbidities and medications should be done to avoid drug-drug interactions. Contraindications for anticoagulation treatment, such as active bleeding or high risk for bleeding, should be excluded. Assessment of bleeding risk factors and the patient's preference are essential when choosing an anticoagulant.

For several decades, VTE in cancer patients was treated solely with LMWH, or in rare situations, with VKAs [321–323]. New treatment options have emerged over the last decade as DOACs have established their place in the anticoagulation treatment of cancer patients [324–326]. The use of DOACs as an initial treatment option for patients with cancer-associated VTE has been compared with LMWH (mostly dalteparin or enoxaparin) in a few trials and meta-analyses. In conclusion, no significant differences in the efficacy or safety have been observed between the treatment regimes, with certain restrictions. [327–332]

The current recommendation is to treat VTE in cancer patients with LMWH once a day, unless patients' characteristics (e.g. risk of bleeding or renal dysfunction) require a twice a day regime. Fondaparinux and unfractionated heparin are alternative options. The DOACs rivaroxaban, apixaban and endoxaban can also be used with a few limitations: adequate renal function, no strong drug–drug interaction with the anticancer treatment and no gastrointestinal absorption impairment. Also, DOACs should be used with caution in patients with genitourinary or gastrointestinal tract malignancies, especially upper gastrointestinal tract malignancies. Incidentally detected VTEs should be treated like symptomatic VTEs although the potential risks of anticoagulation and patient's preference must be considered. [293,311,326,333–335]

The treatment of VTE in cancer patients can also be divided into the acute phase (the first five to ten days after the diagnosis of VTE) which is followed by a treatment period over the next three to six months (a long-term phase) and finally an extended phase (beyond six months). During the acute phase treatment, a vena cava filter should only be considered in case of absolute contraindications to anticoagulant treatment. Similarly, thrombolysis may be considered only rarely on a case-by-case basis, considering contraindications like bleeding risk and brain metastases. [311,326]

After a thorough assessment of antithrombotic therapy, the next challenging decision is the duration of anticoagulation after the treatment period. The initial VTE in cancer patients frequently recurs [67]. The extended use of anticoagulation in cancer patients reduces the risk of VTE recurrence, but it may increase the risk of major bleeding [137,138]. The decision to continue or not to continue anticoagulants (LMWH or DOAC) after six months must be balanced between the benefits and harms, as well as the patients' preferences. Moreover, the duration of anticoagulation should be periodically re-assessed. [311,326,333]

2.6.3 Prevention of VTE in cancer patients

The goal is to identify high risk patients who would benefit from primary thromboprophylaxis. In recent years, different risk assessment models (RAMs) have been developed to guide the decision of VTE prevention in cancer outpatients during systemic anticancer therapy. RAMs are developed to consider clinically identified predictive and risk factors for VTE, including some potential biomarkers that predict the risk of VTE in cancer patients. [336–338]

The Khorana predictive score is probably one of the most internationally validated assessment models for ambulatory cancer patients during chemotherapy. According to the original study, the Khorana score can identify nearly 7% of patients with the risk of symptomatic VTE [24]; in other studies, the risk varies [339]. This risk model incorporates five predictive variables: cancer site, platelet and leukocyte count, hemoglobin level, use of ESAs and BMI, which will score by the risk (**Table 5**) [24].

Table 5. The predictive model (Khorana score [a]) for chemotherapy-associated VTE in outpatients.

Patient characteristic	Points	
Site of cancer		
Very high risk (stomach, pancreas)	2	
High risk (lung, lymphoma, gynecologic, bladder, testicular, renal)	1	
Prechemotherapy platelet count ≥ 350,000/ml	1	
Hemoglobin level < 10 g/dl or use of red cell growth factors	1	
Prechemotherapy leukocyte count >11,000/ml	1	
Body mass index (BMI) ≥ 35 kg/m^2	1	
Interpretation:		**Risk of symptomatic VTE** [a-b]
High-risk score	≥3	6.7–12.9%
Intermediate-risk score	1–2	2.0–3.8%
Low-risk score	0	0.3–1.5%

[a] Modified from Khorana et al. 2008 [24]
[b] Mandala et al. 2012 [339]

A recent systemic review and meta-analysis focused on evaluating the accuracy of the Khorana score. According to the review by *Mulder et al*., only one in four patients with VTE had a high-risk Khorana score, meaning that a substantial amount of cancer patients with VTE could not be identified with the Khorana model [340]. Therefore, other RAMs have been developed. The Prophylaxis of Thromboembolism during Chemotherapy (PROTECHT) score is modified from the Khorana score by adding platinum-based (cisplatin or carboplatin) or gemcitabine chemotherapy to the predictive variables of the Khorana score [341] but it has not yet improved the Khorana score [342]. Also, other score models share the similar structure to the original Khorana score, but in the Vienna Cancer and Thrombosis Study (Vienna-CATS), the score is expanded by adding biomarker P-selectin and D-Dimer [168] and in the CONKO score, BMI is replaced by a World Health Organization (WHO) performance status > 2 [343]. The Prospective Comparison of Methods for thromboembolic risk assessment with clinical Perceptions and Awareness in real life patients–Cancer Associated Thrombosis (COMPASS-CAT) score is developed for ambulatory patients with breast, lung, ovarian or colon cancer. The COMPASS-CAT model takes into account more predictive factors for VTE including patient and cancer-related risk factors (**Table 6**) [71] and therefore it may be more specific to predict the risk of VTE than the other RAMs.

Table 6. Simplified COMPASS-CAT score to assess the risk of VTE in outpatients with breast, lung, ovarian or colon cancer during anticancer therapy. [a]

Predictors for VTE	Points
Cancer-related risk factors	
Antihormonal therapy for women with hormone receptor-positive breast cancer or on anthracycline treatment	6
Time since cancer diagnosis ≤6 months	4
Central venous catheter	3
Advanced stage of cancer	2
Patient-related predisposing risk factors	
Cardiovascular risk factors (composed by at least 2 of the 5 following predictors: personal history of peripheral artery disease, ischemic stroke, coronary artery disease, hypertension, hyperlipidemia, diabetes, obesity)	5
Recent hospitalization for acute medical illness	5
Personal history of VTE	1
Biomarkers	
Platelet count ≥ 350×10^9/L	2
Interpretation:	
High-risk for VTE	≥7
Intermediate/Low -risk for VTE	0-6

VTE: venous thromboembolism;
[a] Modified from Gerotziafas et al. 2017 [71]

The clinical use of different RAMs is still a matter of debate, and comparison of different prediction models is needed. The main problem of current RAMs is that a rather large number of VTEs are diagnosed in patients that are classified as low risk and therefore, better predictive markers are still needed to increase the sensitivity of risk models.

The Ottawa score (**Table 7**) was developed to identify cancer patients with the highest risk of a recurrent VTE. The model includes four independent predictors: gender, primary site of the tumor, stage of cancer and prior VTE. Originally, the model divides risk into two categories, but in the modified score there are three category classes. [344] According to the systemic review and meta-analysis, the modified Ottawa score is a practical tool for assessing the risk or recurrence of VTE within the first six months of anticoagulation [345].

Table 7. The Ottawa Score identifying VTE recurrence risk in cancer patients [a].

Variable	The orginal score points	The modified score points
Female	1	1
Lung cancer	1	1
Breast cancer	-1	-1
TNM stage I	-2	-1
TNM stage II	*NA*	-1
Previous VTE	1	1
Clinical probability		
Low	-3–0	-1 or less
Intermediate	-	0
High	1-3	1 or more

VTE: venous thromboembolism; TNM: tumor classification (T tumor, N Nodes, M metastasis); NA: Not assessed;
[a] Modified from Louzada et al. 2012 [344]

Commonly, the current recommendation is to use LMWH as thromboprophylaxis in cancer patients who are hospitalized with an acute medical condition [311,335] or undergoing major cancer surgery [311,326,333]. During recent years, more data about of the use of anticoagulants, like LMWH or DOACs (mainly apixaban and rivaroxaban), has been accrued for primary thromboprophylaxis of VTE in cancer patients during chemotherapy. As the incidence of VTE decreases during the anticoagulant treatment, the major bleeding complications increase [21–23]. Patients selected with a high risk for VTE (based on the RAMs described above) can be treated with LMWH or DOACs (apixaban and rivaroxaban) for primary thromboprophylaxis of VTE if the bleeding risk is low. Cancer-specific risk assessment tools that also include the risk factors of individual patients are still needed for clinical guidelines. Risk assessment to refine the current risk stratification or the development of new models with promising biomarkers could dramatically change medical practice. [311,326,333,335]

2.6.3.1 Prevention of VTE in pancreatic cancer

Studies have shown that anticoagulant prophylaxis reduces the risk of VTE in patients with PC, although without an OS benefit [346–349]. This may be because prophylactic anticoagulant treatment is not targeted to patients with the highest VTE risk. The different RAMs have been validated to predict the highest risk of VTE among PC patients. The Khorana score or CONKO score have not been able to optimally identify PC patients with a high risk of VTE [350,351], but if the score is

combined with a PTT ratio, it may improve the predictive value [352]. Other biomarkers have also been studied, but even though D-dimers and microvesicle-TF activity are associated with VTE in PC, their predictive value remains uncertain [353]. High fibrinogen and FVIII activity levels are related to PC [233] but more studies are needed to show whether they could be used as predictive factors for VTE in PC patients. Also, high levels of CA 19-9 and carcinoembryonic antigen (CEA) are associated with VTE events in PC patients [354,355] but data on their use in risk assessment is lacking.

2.6.3.2 Prevention of VTE in ovarian cancer

Studies have been undertaken in patients with OC to assess anticoagulant prophylaxis for reducing the risk of VTE [22,356] but the results are not very convincing. Most likely this is because the Khorana scoring poorly predicts VTE in patients with OC [357] and an OC-specific biomarker which predicts for VTE is still lacking. High plasma viscosity preoperatively and during chemotherapy may predict the development of VTE after surgery [358]. Furthermore, preoperative or perioperative elevation of D-dimer value [279,357,359] is reported to be a potential predictive risk factor of VTE in OC patients. Also, a high level of CA 12-5 at OC diagnosis [355], more precisely CA 12-5 level over 500 IU/ml [38], is associated with VTE risk among OC patients.

International guidelines are the same for OC as other cancer types, and they recommend using thromboprophylaxis in cancer patients during hospitalization [311,335] and four weeks following abdominal or pelvic cancer surgery [311,326,333]. Considering the high incidence of VTE among patients with EOC that has been reported prior to surgery and during NACT, it may be necessary to review a change in clinical practice. Therefore, accurate predictors for VTE are urgently needed. D-dimer levels increase in the advancement of EOC stages and high levels are associated with poor prognosis [287,360]. High D-dimer levels may predict VTE, although a cut-off value for specificity and sensitivity is under debate [280,283,287,291]. Also, a platelet count greater than 300 x 10^9 /L preoperatively [283], as well as long prothrombin time (over 11.7 seconds) and high levels of CA 12-5 (over 760 U/ml) [287] are associated with VTE. TF expression has also been shown to be an independent predictive factor of VTE, especially in clear cell carcinomas [30,361].

2.7 Real-world data and biobank

Real-world data (RWD) refers to information relating to patient health and / or delivery health care collected beyond the confines of traditional clinical trials. The data is routinely gathered from a variety of sources that inform health, like electronic

health records (EHRs), national disease registries, billing and prescription databases [362]. The exponential growth in access to data from EHRs, registries and claims databases has expanded and has integrated clinical research into more diverse and real-world settings.

Many current practices, particularly in oncology, are based on the results of several randomized controlled clinical trials where the actual patient population are not being adequately reflected. Among other things, patients with comorbidities and substantial concurrent medication, like elderly and fragile patients are often excluded from the study population. [363] By knowing these limitations, it is difficult to generalize the findings from clinical trials to the large and more inclusive population of patients and to apply them to the everyday management of patients [364,365]. Therefore, RWD is potentially useful for complementing the information from conventional clinical trials.

In the literature, the exact definition of the EHR is variable for its many functions and amounts of clinical data included. In general, EHR contains information regarding a patient during the episodes of care, on the outcomes of care and the continuity of care, documented by various healthcare producers [366,367]. EHRs consist of unstructured, narrative text and structured coded and numeric data and character-based data to images and graphics. Usually, the clinical information is documented in a structured format, including patient data (gender, date of birth) and International Classification of Diseases different Revision (ICD) codes for clinical diagnoses.

EHR is primarily used in daily patient work for planning patient care, the decisions of treatment and documenting on the outcomes of care. The amount and the quality of information from EHR have an impact on the management of care, and in health policy. Furthermore, the data can be used in clinical research, health care management, health services planning and reporting to the government. [366,367] And most of all, the well-documented data in patient care, is a strong foundation to support evidence-based medicine [368].

The growing availability of large sets of EHRs provides unprecedented amounts of clinical data and offers almost unlimited possibilities for different analysis. The rapid evolution in clinical analytics allows techniques for analyzing large quantities of data. This has produced new insights for diseases, identification of clinically meaningful associations and for the construction of predictive models for toward precision medicine [369] and to convert the cost of healthcare [370,371].

The Biobank Act entered into force in Finland on the 1st of September in 2013 [372] and the first clinical biobank, Auria Biobank, was cleared to operate from the National Supervisory Authority for Welfare and Health (Valvira) on March 2014. In Finland, the biobank concept allows the utilization of clinically related information combined with longitudinal EHR information, when linked to a biobank sample or information extracted from it. The data is not limited to hospital discharge diagnoses

but also encompasses all the outpatients treated in the special responsibility area of the hospital. The Biobank Act has significantly increased the biobanks' technical and analytical capabilities related to the use of EHR information within medical research. While the current work is not a biobank study but a registry study, it emphasizes the possibilities that the Biobank Act has created in Finland.

3 Aims

This study was designed to investigate the real-world incidence and time course of VTE in cohort and to evaluate whether laboratory variables in routine clinical care, or clinical features, could predict VTE in cancer patients, especially in patients with PC or HGSOC.

Based on this overall aim, the specific aims of the study were as follows:

1. To evaluate the occurrence of VTE in cancer patients with real-world data
2. To study real-world features associated with VTE in cancer patients
3. To examine the predictive value of clinical features and routine laboratory variables in predicting VTE events in cancer patients, in general
4. To examine the predictive value of clinical features and routine laboratory variables in predicting VTE events in patients with PC or HGSOC

4 Materials and Methods

4.1 Source of data

This retrospective study was based on the analysis of longitudinal EHR information about patients who were treated at Turku University Central Hospital (TYKS). With the authorization of Auria Biobank and Auria Clinical Informatics, the data were collected from several individual EHR datasets that were linked to Turku University Hospital Patient Discharge Data (study I and II). Dates of death were obtained from the Population Register Center. In this electronic database, the clinical data were mostly in a structured form, including patient data (gender, date of birth, date of death), clinical diagnosis codes according to the International Classification of Disease 10th revision (ICD-10)-codes, procedure codes for medical procedures according to national code list, systematic pathology reports (SNOMED) with pathological tumor-node-metastasis (pTNM), the period of intravenous chemotherapy and other interventions like information about hospital pharmacy and radiation therapy. The national code list for medical procedures is based on the Nordic Classification of Surgical Procedures (NCSP), but the Finnish version contains information, e.g imaging and cancer treatment, that are determined by the Finnish institute for health and welfare (THL). All the clinical data e.g the codes, were provided and inserted into EHRs by the patients' responsible physicians at the time of study. A comprehensive set of data, used in the diagnosis and follow-up of patients, clinical chemistry and routinely monitored laboratory values of clinical chemistry and hematology with reference values, were also comprised in the dataset. All individual-level material could be identified accurately to one patient with an encrypted form of a unique personal identification code (social security number). The study I and II were registered and approved by the Turku Clinical Research Center (permission number T133/2013).

In the third substudy (study III), the information about HGSOC patients was obtained a the prospective observational clinical trial of OC (HERCULES, ClinicalTrials.gov Identifier: NCT01276574). The original study was aimed to study drug resistance in HGSOC and was registered and approved by the Turku Clinical Research Center (permission number TO7/009/15), and the Ethics Committee of the Hospital District of Southwest Finland (ETMK): (ETMK 53/180/2009 § 238). All

participating patients gave an informed consent. The research data repository included the following clinical information: the disease stage (basing the staging system by International Federation of Gynecology and Obstetrics 2014 (FIGO 2014)), comorbidities, the routinely monitored laboratory values of clinical chemistry and hematology, the information about cancer treatment (e.g. the treatment strategy, the regimens of anticancer medication, the treatment outcome at different course of the cancer (according to RECIST 1.1 criteria [373] etc.) and survival data. From that dataset, Auria Clinical informatics collected the data, and it was complemented by the information gathered from the hospital electronic database, corresponding to the aims of study III.

4.2 Study population

The study populations for all three substudies were retrospectively collected comprising adult patients (age 18 years and over) treated at TYKS from 2005 to 2013 (study I), from 2004 to 2013 (study II) and from 2009 to 2020 (study III).

4.2.1 Diagnosis of VTE

In- or outpatients who were treated for VTE events as the main or secondary diagnosis during the follow-up period of each study, were selected from the electronic database according to the following ICD-10 codes: ICD-10 Code I80* and I82* for DVT, ICD-10 code I26 for PE and ICD-10 code I81 for PVT. Each VTE diagnosis was reconfirmed in studies II and III from the individual electronic medical patient record. Only VTE diagnoses that were based on radiologic imaging were included. The approved method of radiologic imaging was compression ultrasound for DVT; CT, pulmonary angiography, or ventilation-perfusion lung scan for PE; and CT or ultrasound for PVT. Any suspicion of VTE without radiologic imaging was excluded. Patients with superficial thrombophlebitis or a strong suspicion of VTE but with no radiological evidence of deep VTE, were transferred from the VTE group to the control group (non-VTE group). In the study I, VTE diagnoses were based merely on the presence of the ICD-10 codes.

4.2.2 Cohort selection (I)

The study I population comprised all patients who were treated in TYKS that were either in- or outpatients from 1.1.2005 to 31.8.2013. Patients diagnosed and treated for VTE during that period were selected from the hospital electronic database using the ICD-10 codes, as described above. Patients' comorbidities were also defined according to the ICD-10 codes and were listed into the larger categories based on

vital organs and disease groups, adapting for the medical classification by the ICD-10. To comprehend the real-world setting of the incidence of VTE events in different disease groups, patients with VTE were age- and gender matched with a 5-fold control population (as possible) with the same diagnosis codes of chronic diseases but without the ICD-10 code of VTE in the medical history of EHR. For further analysis to focus on chemotherapy treated cancer patients and VTE, the information about cancer diagnosis (ICD-10 codes (C00*–C97*)) and chemotherapy data from hospital pharmacy were combined. For statistical analyses, cancer types were only chosen if there were over 100 patients' data available during the period. By utilizing the hospital pharmacy database, from those cancer patients, patients were identified that were treated with platinum-based chemotherapy. Furthermore, by using the ICD-codes C78*–C79* for distant metastasis, the advanced stage disease could be determined in cancer patients that were included in further analyses.

4.2.3 Pancreatic cancer patients (II)

In study II, all patients with ICD-10 codes of VTE and metastatic or locally advanced PC (ICD-10 codes of C25*) at the hospital electronic database during the period from January 2004 to December 2013, were screened eligible for the study. The diagnoses of both cancer and VTE were manually verified from an individual's electronic medical patient record. Inclusion criterion was a metastatic or locally advanced adenocarcinoma of the pancreas, and the diagnosis was either histologically confirmed or based on strong clinical findings, such as the combination of elevated levels of plasma CA 19-9, radiologic imaging and the time course of disease. Additionally, VTE was diagnosed radiologically after the diagnosis of PC. PC patients with VTE were confirmed from the dataset, and a gender-, cancer stage- and age-matched control PC patient without VTE was identified. Also, from the control PC patient, the diagnoses of cancer were manually confirmed and at the same time, it was verified that there were no VTE events in their medical history.

4.2.4 High-grade serous ovarian cancer patients (III)

In study III, all patients diagnosed with HGSOC and enrolled into the clinical trial (as described above) during the period 1.1.2009–28.2.2020 were screened for eligibility in the study. The total follow-up time ended 31.8.2020, and each patient was followed-up at least six months after the HGSOC diagnosis. From the research data repository (n=233), only HGSOC patients with comprehensive clinical and EHR data available during the entire follow up period were included in study III. HGSOC patients whose chemotherapy and follow-up were conducted in hospitals

other than TYKS (*e.g.* regional and central hospitals) were therefore excluded (n=85).

4.3 Co-variates

4.3.1 Study I

Among the cancer patients treated with chemotherapy, the co-variates included were age at initiation of chemotherapy, gender, laboratory values starting three months before the first dose of chemotherapy, distant metastases, radiotherapy (for neoadjuvant, adjuvant, radical or palliative intent) and platinum-based chemotherapy (for neoadjuvant, adjuvant or palliative intent). Also, the surgery procedure, where tumor tissue was surgically removed partly or completely, was included as a co-variate. The surgery was either for curative or palliative intent. The laboratory values were included if the test was performed in at least 80% of the patients both within three months before chemotherapy and during chemotherapy (**Table 8**).

4.3.2 Study II

Of the routinely monitored laboratory values of clinical chemistry and hematology, blood count and CA 19-9 (kU/L) were available for most of the patients in study II and were therefore included in the co-variates of the study **Table 8**

4.3.3 Study III

All the laboratory blood samples collected during the treatment and follow-up visits as a part of routine clinical care, were included (**Table 8**). The comorbidities were classified into five groups based on vital organs and disease groups according to medical classification by a modified ICD-10. The BMI was recorded at the time HGSOC was diagnosed. The treatment strategy was either PDS or IDS performed following platinum-based NACT. The PFI was defined as a time of platinum-free months from the date of last platinum-based chemotherapy dose until the date of progression or death, whichever followed first. Continuous attributes were described using medians with upper and lower quartiles and categorical attributes using proportions.

Patients whose VTE were diagnosed before HGSOC diagnosis (n=5) were excluded from further statistics analysis due the lack of co-variates data before VTE diagnosis.

Table 8. The laboratory measurements of clinical chemistry and hematology included in the studies.

	Study I	Study II	Study III
Platelet count	x	x	x
Hemoglobin level	x	x	x
Leucocyte count	x	x	x
Neutrophil count	x		x
Erythrocyte mean cellular volume	x	x	
Erythrocyte mean corpuscular hemoglobin	x	x	
Hematocrit	x	x	
Plasma creatinine	x		x
Plasma alanine transaminase	x		x
Plasma alkaline phosphatase	x		x
Plasma sodium	x		
Plasma potassium	x		
Plasma levels of carbohydrate antigen-19-9 (P-Ca 19-9)		x	
Plasma albumin			x
Plasma levels of carbohydrate antigen-12-5 (P-Ca 12-5)			x

4.4 Statistical analyses

In studies I and II, all the statistical analyses were performed using R Statistics V.3.0.2 with standard packages R Core Team (2013) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. In study III, the analyses were conducted with R software version 3.6.3 (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org).

In study I, the X^2 test was used to calculate relative risks (RR) for comparing the proportions of patients with VTE to patients without VTE between different groups of diseases. Kaplan-Meier analysis was used to assess the time to VTE in all studies and the VTE-free time was calculated from the beginning of chemotherapy (study I) or from cancer diagnosis (study II and III) to documented VTE event or patient's death or the end of follow-up, whichever occurred first. Also, the OS was explored with the Kaplan-Meier estimator and the differences in survival distributions were compared using the log-rank test in study III. The median OS and median time to VTE with the 95% confidence intervals (CIs) were provided if reached. P-values under 0.05 were considered statistically significant.

The patient characteristics between VTE and patients without VTE, were tested using the Fisher's exact test for categorical attributes and the Mann-Whitney U test for continuous attributes (studies II and III). Continuous laboratory values were

dichotomized into categorical variables according to the cut-off values with a maximum sum of sensitivity and specificity. The risk factors of VTE were analyzed using the Cox proportional hazard models, both the univariate model and the multivariate model (study I-III). The Cox proportional hazard model results were presented as hazard ratios (HRs) with the corresponding 95% Cls. The Cox model time scale included follow-up time from the first chemotherapy treatment (study I) or from the time cancer was diagnosed (study II-III) to the date of VTE diagnosis, or date of death or the end of the study's follow-up. Also, the Schoenfeld residuals were used to verify the proportional hazards assumption and the nested models were compared using the likelihood-ratio test (study III). Receiver operating characteristic (ROC) curves alongside of 95% CIs were produced to explore the specific application to the choice of optimal laboratory variables on predicting VTE (Study I) and the optimal cut-off point at which CA 19-9-DT was predicting VTE (Study II).

To describe the exponential increase of CA 19-9 (study II) and of CA 12-5 (study III) after cancer diagnosis, the marker's doubling time (DT) was conducted using all the available values of CA 19-9 or CA 12-5 after cancer diagnosis. The DTs were constructed by fitting a linear model for the logarithm of CA 19-9 or CA 12-5 values and by dividing log 2 by the slope of the regression line. In study II, the Spearman's correlation coefficient was used to measure the strength of association between CA 19-9-DT and VTE event.

5 Results

5.1 Patients' characteristics

In study I, the database search contained overall information about 495 089 patients (**Table 9**). The VTE diagnosis was found in 5 452 (1.1%) patients of whom 1 467 also had a cancer diagnosis. The other most common diagnoses associated with VTE were hypertension (n=2 296), coronary heart disease (n=1 437), congestive heart failure (n=1 091), atrial fibrillation/flutter (n=999) and diabetes (n=869). The ICD-10 codes of VTE were not classified separately as DVT, PE or PVT in the frame of this research setting.

In study II, 164 patients with PC were originally enrolled to the study, with 83 patients having an ICD-10 code of VTE and 81 patients without VTE (**Table 9**). Some of the patients were reclassified or excluded due to missing follow-up data, incorrect documentation of the ICD-10 codes or uncertainty of the diagnostic accuracy (for cancer or VTE). For example, twelve patients were excluded due to unconfirmed cancer diagnosis and in fifteen patients the cancer was not originally in the pancreas. Seven patients with PC had a radiologically verified VTE diagnosis incidentally on routine CT during normal follow-up examination but the ICD-10 code of VTE was unreported on the patients EHR. These patients were reclassified to the VTE group. Also, six patients were excluded from the VTE group because three patients only had clinical diagnosis of VTE (no radiologic imaging was done) and three patients had no radiologically verified VTE (although the clinical probability of VTE was strong). Therefore, for the final analysis, 58 PC patients with VTE and 50 PC patients without VTE were included (**Table 9**). The age (mean ± SD) of the VTE patients with PC was 68.1 ± 11.6 years and of the control patients 71.7 ± 10.9 years.

Also in study III, some patients were removed from the original study population (n=148) (**Table 9**). Two of the patients' follow-up data was inadequate and therefore they were excluded from the study. Six patients with HGSOC had a radiologically verified VTE diagnosis incidentally on routine CT during normal follow-up examination but the ICD-10 code of VTE was not reported on the EHR. These patients were reclassified to the VTE group. Furthermore, seven patients with the ICD-10 code of VTE but no evidence of the VTE event in their medical history

before or during the HGSOC, were removed from the VTE group. One patient received only palliative care and was excluded from inferential statistics. The median age (IQR) of all patients with HGSOC was 60.0 years (62.0–74.0) and of patients with VTE, the median age was 65.0 years (60.5–71.0).

Table 9. The study populations in studies I-III.

	Study I	**Study II**	**Study III**
Hospital	Turku University Hospital	Turku University Hospital	Turku University Hospital
Study perioid	1.1.2005 – 31.8.2013	1.1.2004 – 31.12.2013	1.1.2009 – 31.8.2020 [a]
Number of patients	495 089	164 (108) [b]	148 (146) [b]
Number of VTE patients	5452	83 (58) [b]	30 (24) [b]
The characteristics of VTE patients		n = 58	n = 24
Asymptomatic VTE	*NA* [c]	5 (9%)	6 (25%)
DVT (%)	*NA* [d]	39 (67%)	13 (54%)
PE (%)	*NA* [d]	17 (29%)	11 (46%)
PVT (%)	*NA* [d]	2 (4%)	0 (0%)
The median time of VTE after cancer diagnosis	*NA*	2.5 months	12.8 months

VTE: venous thromboembolism; NA: not assessed; DVT: Deep venous thrombosis; PE: Pulmonary embolism; PVT: Portal veins thrombosis

[a] Including at least six months follow-up time from the HGSOC diagnosis (Only patients who were diagnosed HGSOC by 28.2.2020 were included)

[b] Some of the patients were reclassified or excluded due to missing follow-up data, the incorrect documentation of ICD-10 codes or uncertainty of the diagnostic accuracy (for cancer or VTE)

[c] merely ICD-codes do not classify whether VTE was symptomatic or asymptomatic: this research setting was based only ICD-codes

[d] all ICD-10 codes of VTE were grouped together and therefore VTE events were not classified separately as DVT, PE or PVT

5.2 VTE in cancer patients (I)

To analyze the VTE's relative risk, 5-fold control group age- and gender- matched without the ICD-10 code of VTE in medical history was collected, overall, 27 260 patients. An increased risk was seen in most of the chronic diseases, including cancer (RR 1.52, Cl 1.45–1.60, $p < 0.001$). The overall incidence of VTE was 3.5% among all cancer patients (n=42 245) and it varied between the different cancer types (**Figure 3**). The highest incidence was seen in mesothelioma (6.8%), gastric cancer (6.0%), OC (5.7%) and PC (5.5%) whereas the lowest rates occurred in melanoma (2.6%) and testicular cancer (1.7%).

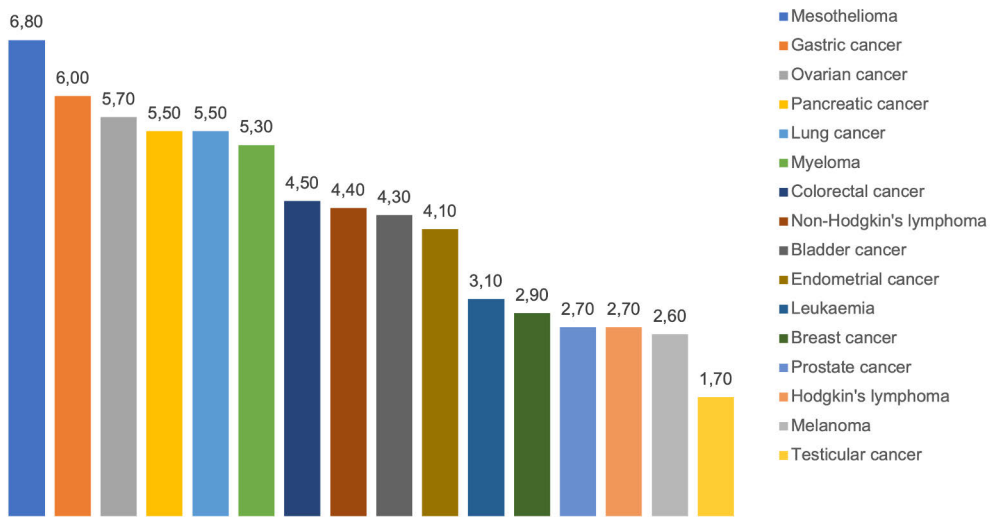

Figure 3. The incidence (%) of VTE in 16 malignancies.

5.3 Incidence and risk factors of VTE during chemotherapy (I)

Overall, the study I contained information of 7 778 cancer patients who were treated with chemotherapy during their disease. The VTE was diagnosed in 282 (3.6%) patients, with a median time of 7.3 months from the onset of chemotherapy to VTE diagnosis. The rate of VTE events varied in different cancer types, and based on the Kaplan-Meier analysis of VTE-free time after the onset of chemotherapy, the risk of VTE could be classified into three groups (**Table 10**).

The risk of VTE was increased by distant metastases (HR 1.89, 95% Cl 1.40–2.53, $p < 0.001$) and platinum-based chemotherapy (HR 1.77, 95% CI 1.40–2.24, $p < 0.001$). The VTE risk was associated with values of laboratory variables: platelet count ($> 316 \times 10^9$/L), leukocyte count ($> 6.3 \times 10^9$ cells/L), neutrophil count ($> 3.3 \times 10^9$ cells/L) and plasma creatinine (> 62.5 µmol/L), but in the multivariate Cox analysis, only elevated neutrophil count (HR 1.96, 95% Cl 1.33–2.89, $p < 0.01$) and plasma creatinine level (HR 1.60, 95% Cl 1.21–2.21, $p = 0.001$) were associated with the increased risk of VTE.

Table 10. The risk of VTE based on - VTE-free time after the onset chemotherapy.

High risk	Medium risk	Low risk
Pancreatic cancer	Myeloma	Hodgkin's lymphoma
Lung cancer	Endometrial cancer	Breast cancer
Ovarian cancer	Gastric cancer	Bladder cancer
Mesothelioma	Melanoma	Leukaemia
	Colorectal cancer	Testicular cancer
	Non-Hodgkin's lymphoma	
	Prostate cancer	

5.4 CA 19-9 as a predictor of VTE in pancreatic cancer (II)

Of the laboratory variables, only decrease in the median change of the red blood cell count ($p = 0.05$) and increase in CA 19-9 ($p = 0.004$) were associated with VTE events in PC patients. However, both the patients with VTE and non-VTE were observed to have high levels of CA 19-9 (over 10 000 kU/L). A more detailed analysis, where CA 19-9-DT described the exponential increase of CA 19-9 after the PC diagnosis, showed that the median doubling time of CA19-9 value was almost 6-fold shorter in patients with VTE (2.7 months) than non-VTE patients (16.1 months). Based on the ROC analysis, the maximum sum of sensitivity and specificity of CA 19-9-DT for predicting the VTE was at 4.4 months, with sensitivity 0.65 and specificity 0.74. Patients with CA 19-9-DT < 4.4 months were categorized as the high-risk group, with a 55% probability of a VTE event within 12 months, whereas patients in the low-risk group (CA 19-9-DT > 4.4 months) had a probability of VTE at 23%. The risk of VTE was 3-fold higher in patients in the high-risk group (HR 3.00, 95% Cl 1.25–7.19, $p < 0.010$).

No statistically significant difference in median OS between patients with or without VTE was seen.

5.5 Clinical and laboratory variables associated with VTE in high-grade serous ovarian cancer (III)

At the time of HGSOC diagnosis, the median CA 12-5 values were higher among patients who later developed VTE ($p = 0.01$), but other laboratory variables did not differ between the patients with VTE and non-VTE. VTE was more common in NACT-treated patients than in the PDS group (OR 5.6, Cl 95% Cl 1.50–31.7, $p = 0.005$).

In multivariate model analysis, PFI was associated with VTE. The risk of VTE was reduced by 16.9% for every platinum-free month (HR 0.84, 95% CI: 0.74–0.96, p = 0.013). Of the laboratory variables, higher hemoglobin (HR 0.95, 95% CI: 0.93–0.97, p < 0.001) and higher albumin levels (HR 0.90, 95% CI: 0.83–0.98, p = 0.015) decreased the risk of VTE whereas higher leukocyte count (HR 6.05, 95% CI: 1.78–20.57, p = 0.004), neutrophil count (HR 3.81, 95% CI: 1.33–10.92, p = 0.013) and CA 12-5 (HR 1.79, 95% CI: 1.35–2.38, p < 0.001) were associated with the increased risk of VTE events. A more detailed analysis showed the CA 12-5-DT described the exponential increase of CA 12-5 after the HGSOC diagnosis and in patients with VTE the median CA 12-5-DT was shorter than in non-VTE patients (8.75 months versus 12.5 months). The cut-off values for the individual variables to predict VTE risk was not established.

The survival of the patients with VTE was significantly shorter than patients with non-VTE (p = 0.010). The median OS for patients with VTE was 30.6 months (95% CI: 18.20–NR) whereas for the patients without VTE the median OS time was 41.6 months (95% CI: 33.94–60.48).

6 Discussion

The purpose of this study was to identify potential and promising clinical markers that could predict VTE in patients undergoing cancer treatment. Therefore, patients with a considerable risk of VTE could be better identified in the future, and subsequently offered an individual thromboprophylaxis treatment. This strategy would potentially decrease the incidence of VTE and improve the survival and quality of life of cancer patients.

6.1 Retrospective nature of the data

The exponential growth in access to data from EHRs and registry databases has expanded and integrated clinical research into more diverse and real-world settings. In studies I-III, linking of multiple datasets enabled evaluation of the incidence of VTE and assessment of risk factors associated with VTE in cancer patients in a real-world setting. The studies have limitations due to the retrospective nature of the data and dependence on the routinely collected data as part of clinical care. Therefore, some interesting data was missing, e.g. BMI at the time of VTE diagnosis and the laboratory values of D-dimer, prothrombin fragment 1+2 and factor VIII [170].

The timing of laboratory tests and treatments were not standardized, which may explain the discrepancy between the results of this study and previous studies. The patients were not routinely scanned for VTE in any of the studies I-III. Therefore, certain asymptomatic VTE cases might have gone unnoticed. However, given the association between cancer treatments and increased risk of VTE documented in previous literature [12,13,26,71,143,227–229,277,289,291,292], and the consistent monitoring of patients through medical imaging and clinical examinations conducted by physicians, it can be posited that the likelihood of these occurrences escaping detection is minimal. On the other hand, the studies were able to observe clinically meaningful associations with VTE that may have remained otherwise unnoticed, such as CA 19-9-DT in PC patients and short PFI in HGSOC.

The real-world setting in studies II and III revealed that the documentation in EHRs varies and the ICD-10 codes are not consistently documented. However, there are no exact definitions of diseases or standards for the use of ICD-10 codes. The main problem is probably that ICD-10 codes are used while the diagnostic tests are

only upcoming; in other words, the diagnosis is just a suspicion. Therefore, the diagnosis may change after the final test results, but the original ICD-10 code remains at the patients' EHR and the new ICD-10 code is added after the final diagnosis. This is understandable because according to common practice, the physician typically uses a preliminary ICD-10 code in the EHR while still waiting for the final test results. On the other hand, the physician may also forget to record the correct ICD-10 code in the patients EHR, although the disease (e.g, VTE) will be accurately treated. Nevertheless, as the use of the information from EHRs and registries is set to increase, there should be some standards and structure for reporting the EHR that may require further validation. This would improve the data quality and collection for secondary use in clinical research.

6.2 Incidence of VTE in cancer patients

The results of the studies I-III further corroborated the strong association between cancer and VTE that is described in the literature and in previous studies. In study I, the overall incidence of VTE was 3.5% in all cancer patients (n=42 245) which is relatively in line with the other studies. Remarkably, the result was very similar to that reported by *Betts et al.* in a large network meta-analysis that involved almost four million cancer patients, where 3.1% of patients were diagnosed with VTE within a year of cancer diagnosis [374].

In the other studies, the incidence rate for VTE with cancer patients has been reported to vary widely from 0.5% to 20% [13,25,26,126,136] and the variation may be explained by differences in the cohort populations. Hematologic malignancies and brain tumors have occasionally been excluded, whereas some other studies have focused only on the chemotherapy treated cancer patients. Also, some patients were excluded from previous studies if VTE was the first symptom of cancer. Nevertheless, the highest incidence rates of VTE are reported associated with malignancies of ovary, pancreas, brain, stomach and lung [13,25,26,124–126] which is in line with the results of our study I.

However, the incidence of VTE in HGSOC patients was relatively high (16%) in study III compared with previous studies (3–8%) [37,275,288]. One likely explanation for the high incidence rate is that the cohort of study III comprised mainly of patients with advanced disease (FIGO III-IV), which is a well- known risk factor for VTE [274,289,375] and is very common among HGSOC patients [239,246]. Similar VTE incidence (12%) was observed in the meta-analysis by *Weeks et al.,* where VTE was diagnosed in 769 out of 6 324 patients with OC [281]. In conclusion, it appears that in general, biologically aggressive cancer types with early metastatic spread and poor prognosis are associated with a high incidence of VTE.

6.3 VTE and chemotherapy

6.3.1 Platinum-based chemotherapy and VTE

The highest incidence rates of VTE are documented after cancer diagnosis and during chemotherapy [13,27,130] and therefore study I focused on chemotherapy-treated cancer patients. The risk of VTE was increased by platinum-based chemotherapy in univariate analysis; however, we were not able to itemize which platinum-agent (cisplatin, oxaliplatin or carboplatin) may have influenced the risk assessment. Cisplatin- and carboplatin-containing regimens are associated with a higher risk of VTE [131,151–153] but data on the oxaliplatin-containing regimens is not so unambiguous [154].

On the other hand, study III showed that in HGSOC patients, VTE was more common in NACT treated patients than in the PDS group, even though the same platinum-based regimens were used for both NACT and adjuvant chemotherapy. This result is in line with other studies, where almost a fourth of the OC patients who underwent NACT developed VTE during chemotherapy [277] and nearly half of them were diagnosed before interval debulking surgery [273]. It is recommended to use LMWH as extended thromboprophylaxis after cancer surgery [311,326,333] which may have reduced the risk of VTE during adjuvant OC chemotherapy. When adjuvant chemotherapy begins after PDS, as much of the cancer as possible has already been removed by surgery. At the beginning of NACT, on the other hand, risk factors for VTE (e.g. metastasis, ascites and /or large tumor causing stasis and blood flow slowdown) are more likely. HGSOC cells can activate the coagulation cascade causing a hypercoagulability state [28,30,31] which also increases the risk of VTE. Therefore, thromboprophylaxis during NACT in HGSOC patients should also be assessed prospectively [376]. It is already recommended to consider LMWH [311] or optionally DOACs [326,333] for VTE prophylaxis in ambulatory patients with locally advanced or metastatic pancreatic cancer during first-line systemic anticancer treatment.

6.3.2 Platinum-free-interval and VTE in high-grade serous ovarian cancer patients

A very fascinating finding was that a short PFI was associated with VTE risk in HGSOC patients (study III). Platinum-based chemotherapy is the backbone of treatment for HGSOC [268,270–272] whereas PFI is one of the prognostic factors for response to treatment and survival in OC [269,377,378]. Traditionally, if HGSOC relapses (or progresses) within six months of the last platinum dose, it is considered platinum resistant [379,380]. *Gerotziafas et al.* reported in the COMPASS-CAT study an increased risk of VTE in cancer patients with partial or no response to treatment, compared

with patients reaching complete remission [71]. Research is undergoing to understand and explain the molecular mechanisms leading to platinum resistance [381] ; a phenomenon which may cause aggressive cancer biology, poor prognosis and increased risk for VTE.

Several mechanisms probably underlie the link between PFI and increased VTE risk in HGSOC patients, including the complex interplay between coagulation systems and cancer cells. Cancer cells activate coagulation that promotes the development of VTE [382]. At the same time, activation of the clotting system may also have several roles in tumor growth, angiogenesis and invasion and therefore affect cancer progression [383–385]. This may result in early relapse and a short PFI. It has been speculated that anticoagulants, e.g. LMWHs, may have beneficial effects in OC patients; not only by preventing or treating VTE, but also through potentially modifying effects on cancer biology [386–388] and platinum resistance [386]. It is possible that especially HGSOC patients with a short PFI could benefit from targeted thromboprophylaxis, but more clinical trials are needed to validate this hypothesis.

6.4 Predictive clinical variables and biomarkers of VTE

Routine parameters that are usually available at initial diagnosis, treatment and follow-up of every cancer patient, are the most practical and cost-effective (no additional costs) for the assessment of VTE risk. Therefore, the first and probably most widely referred Khorana score has created the basis of a clinical decision model that guides VTE risk assessment in oncologic patients [24]. However, it has been proved beyond doubt that the Khorana model is not perfect, and its' reproducibility is poor [340]. The pooling of unique datasets from various longitudinal EHRs that were used in studies I-III provided a practical tool for identifying clinically meaningful associations and laboratory variables as risk factors for VTE.

6.4.1 Advanced cancer stage

Distant metastases increased the risk of VTE in study I. This is in line with other studies where the risk of VTE has been reported as 2 to 20-fold with distant metastases, compared to the early stages of disease [12,26,27,71,123,126,141,164,228]. In study III, most of the HGSOC patients (94%) had advanced disease stage (FIGO III–IV) which is consistent with real-life data. Patients with metastases have been described to have higher levels of D-Dimer and platelets and lower hemoglobin levels, compared to patients with local and early stages of disease [389]. These factors may increase hypercoagulability and further increase the risk of VTE. On the other hand, early metastatic spread and short survival time usually correlate with biologically

aggressive cancer types, which may reflect that the incidence of VTE is also associated with biological aggressiveness of cancer.

6.4.2 Routine laboratory parameters

During anticancer treatment, patients are consistently monitored through laboratory tests, radiologic imaging and clinical examinations. Therefore, in all the studies I-III, the laboratory variables played a role in predicting VTEs in cancer patients in general (study I) and specifically in patients with PC (study II) or HGSOC (study III).

In study I, over ten laboratory values were evaluated for their capacity to prefigure VTE events during chemotherapy, and only elevated neutrophil counts ($> 3.3 \times 10^9$ cells/L) and plasma creatinine levels (> 62.5 μmol/L) were statistically associated with an increased risk of VTE. A similar result was seen in study III where the elevated leukocyte and neutrophils counts were associated with an increased risk of VTE in HGSOC patients. Although the results of studies I and III were not completely similar to the Khorana score [24], the findings were fascinating considering the new insights into the pathogenesis of VTE.

Recent studies have indicated that the inflammatory response has a role in the pathogenesis of VTE in general [390–392]. Especially, neutrophils might mediate this pathogenesis [393,394] and as previously described, NETs are associated with cancer-associated thrombosis [179,180]. The interaction between neutrophils and platelets is observed in arterial thromboinflammation [395] which may have a role in the formation of thrombus in veins as well. Therefore, it is possible that platelets and leukocytes, especially neutrophils, increase the risk of VTE, but further studies are needed to evaluate the adjusted cut-off values.

Unlike previous studies [24,71,163,165,283,341], the correlation between platelet counts and VTE was not seen in any of the studies I-III. In study III, the HGSOC patients who later developed VTE had thrombocytosis (platelet count above 350×10^9/L) at the time of HGSOC diagnosis, but the difference to non-VTE group was not significant ($p = 0.68$). Noteworthy, the timing of platelet counts, and the treatments were not standardized, which may explain this discrepancy.

Abnormal level of hemoglobin is a well-documented risk factor for VTE in cancer patients [24,168,291,341,343], but we found an association between decreased hemoglobin level and VTE only among HGSOC patients in study III. Iron deficiency anemia has been reported to associate with thrombosis risk in general population [396,397]. Iron deficiency may induce thrombocytosis and lead to a hypercoagulable state [398,399], but the exact mechanism is unknown. The prevention and treatment of anemia, whether stemming from causes such as iron deficiency, hemolysis, or myelosuppression, may reduce the likelihood of thrombosis events.

In study I, elevated plasma creatinine level (> 62.5 μmol/L) increased the risk of VTE but unfortunately, the functional renal assessment commonly used was not available in the study frame. Currently, there are some contradictory results whether a reduced estimated glomerular filtration rate (eGFR) increases the risk of VTE [400] or not [401]. Results reported by *Ferroni et al*. showed that a reduced eGFR, even with normal serum creatinine values, was associated with an increased risk of VTE in cancer patients [400]. However, in a study of a large cohort of cancer patients by *Königsbrügge et al,* a reduced eGFR was not seen as a risk factor for VTE [401]. In a study that was conducted with non-cancer-patients, decreased renal function (eGFR 16–59 ml/min) increased the risk of VTE about two-fold compared to patients with normal renal function [402]. Further studies are needed in a cancer-specific population. The validity of renal dysfunction as a risk factor for VTE might be minor in cancer patients compared to non-cancer patients but may be more useful for treatment decisions. In fact, none of the risk models have yet included serum creatinine value or eGFR as a part of risk scoring [24,71,163,165,168,283,341].

Notably, all risk factors for VTE are often found in combination and act synergistically. To summarize, elevated leukocyte, especially neutrophil counts, and decreased levels of hemoglobin should be considered in further elucidation or validation of risk assessment models for predicting VTE in cancer patients.

6.4.3 CA 19-9-doubling time in pancreatic cancer

CA 19-9 is a well-defined biomarker and predictive marker of PC, and it is routinely followed during the course of disease [213,216,217]. Increased levels of serum CA 19-9 have been associated with VTE events in PC patients [354,403], but the unique finding in the present study was that a short CA 19-9 doubling time (19-9-DT) was a good predictor for VTE (study II). The median CA 19-9-DT after PC diagnosis was almost 6-fold shorter with patients with VTE than patients without VTE. Noteworthy, both patient groups (with and without VTE) were observed to have high levels of CA 19-9, but unlike previous studies, the absolute elevated values were not associated with VTE risk. The presence of jaundice was not taken into account, which may have increased the levels of CA 19-9 [213] and might have interfered with the interpretation.

Study II was based on case-controls and the patients were matched for the stage of disease, so advanced disease was not a confounding element. Therefore, the exponential increase of CA 19-9 may refer to the progressive mechanism of venous thrombosis and renders the interaction between CA 19-9 and coagulation as a target for further studies. Patients with CA 19-9-DT less than 4.4 months had a 3-fold risk of VTE. It is possible that PC patients with a short CA 19-9-DT may benefit from targeted thromboprophylaxis; however more clinical trials are needed to validate this

hypothesis. Moreover, the interaction between CA 19-9, thrombosis and hemostasis is also an important area for future research.

6.4.4 CA 12-5 in high-grade serous ovarian cancer

The cancer biomarker CA 12-5 is routinely used in EOC to diagnose, monitor response to treatment and detect recurrence [261,404]. Commonly, increased level of CA 12-5 is a sign of progression in EOC [373] but it may also predict VTE [38,291]. Findings of study III, where higher CA 12-5 level and a short CA 12-5 DT were associated with an increased risk of VTE event in HGSOC patients, are in line with other studies.

The correlation between elevated CA 12-5 level and high D-dimer values has been described in EOC patients [405] It may reflect hyperactivation of the fibrinolytic pathway in the presence of tumor load, also with HGSOC patients. According to a phase II randomized study, prophylactic LMWH (dalteparin) reduced the serum CA 12-5 levels in EOC patients. However, the study frame lacked an appropriate control group and the trial was prematurely concluded [406] so major conclusions cannot be made.

CA 12-5 may be linked with coagulation activity in advanced EOC, but it awaits further study. In particular, the role of CA 12-5 in the pathogenesis of VTE needs further elucidation. Therefore, based on previous studies and our findings, HGSOC patients with higher values of CA 12-5 and a short CA 12-5 DT have an increased propensity to develop VTE but further information of the correlation between CA 12-5 and VTE risk required.

6.5 The value of studies in everyday practice

Risk-directed primary thromboprophylaxis is an appropriate approach for cancer patients [407]. Risk prediction of cancer-associated VTE is a compelling challenge in oncology, as VTE may result in cancer treatment delays, impaired quality of life, and increased morbidity and mortality. The findings of this study add to the growing understanding of cancer-associated VTE. Study I showed that VTE is common in cancer patients, especially in adenocarcinomas and during chemotherapy. The percentage of asymptomatic VTEs in all patients was 9% in study II and 25% in study III. It is not clear, how many of these VTEs were really asymptomatic. Patients may have had some symptoms (e.g. fatigue, dyspnea) which were easily attributed to underlying cancer or it's treatment.

The patients are usually well-informed about the most common complications of cancer therapy, e.g. febrile neutropenia during chemotherapy, immunotherapy-associated autoimmune diseases etc. However, risks and symptoms of VTE are

probably easily overlooked in the education of cancer patients. Furthermore, the risk assessment models to design individualized thromboprophylactic approaches are not (yet) routinely utilized. Therefore, it is necessary to increase awareness, and perhaps it is time to develop a concise national recommendation focusing only on cancer-associated VTE.

6.6 Future studies

Currently, patients with locally advanced or metastatic pancreatic cancer on anticancer therapy, are recommended to use LMWH or DOACs (apixaban and rivaroxaban) for primary thromboprophylaxis of VTE if the bleeding risk is low. [326] However, not all patients benefit from this approach and individualized risk assessments are needed. More studies are necessary to evaluate the efficacy and safety of primary prophylaxis during different chemotherapeutic regimens and with different types of cancer. Furthermore, cost-effectiveness studies are also needed. It is also desirable that authorities approve apixaban, rivaroxaban and/or LMWH for thromboprophylaxis in outpatients with cancer.

Based on the latest studies, different hemostatic biomarkers, mostly D-dimer and fibrinogen, represent promising variables for potential clinical implementation in risk assessments for VTE in patients with cancer [408]. Also new point of view are NETs that are associated with cancer-associated thrombosis [179,180]. The ability of neutrophils to form NETs was first reported as a defence mechanism against microbial pathogens by Brinkmann et al [409]. Later, it was noticed that NETs have prothrombogenic and platelet-activating properties in animal models [410]. Also, malignancy can predispose neutrophils to form NETs leading to cancer-associated thrombosis [179]. Recent studies have showed that high plasma levels of a NET biomarker, citrullinated histone H3, increase VTE risk [411] and are associated with poor prognosis in patients with advanced cancer [412]. Therefore, biomarkers reflecting NET formation could prove beneficial to predict thrombosis risk in the future, but more information is still needed from clinical practice and interventional studies.

While many potential biomarkers have already been identified, selection of candidate biomarkers requires the consideration of scalability and practicality as they proceed from research to clinical practice. Biomarkers and associated models must be simple enough to encourage clinical use, but also perform reliably enough to improve clinical outcomes in preventing VTE. [413]

Cancer treatments are more and more complicated, and oncologists must combine several individualized approaches to personalize cancer care. Therefore, it would be valuable to develop artificial intelligence (AI) algorithms that could assist in predicting VTE risk individually, and to utilize personalized decision making. [414] Many clinical features and laboratory variables already recognized as potential risk

factors for VTE are suitable for computational analysis and could probably be utilized to predict VTE in cancer patients. Studies in the future may show that AI, and in particular machine learning methods, can combine different data to predict VTE individually and to identify the best treatment option (DOAC versus LMWH) so that the oncologist can be focused on active cancer therapy. The improvement of risk assessment models for cancer-associated VTE in combination with AI methodologies and deep learning techniques are promising tools for the future.

7 Conclusions

The main conclusions of this thesis are:

1. VTE events are common in cancer patients; every fourth VTE diagnosis is associated with cancer. According to our study, the highest incidence of VTE was seen in patients with mesothelioma and adenocarcinomas, especially gastric, pancreatic, lung and ovarian cancers.

2. VTEs were most common in cancer patients with distant metastases and those receiving platinum-based chemotherapy. Also, elevated neutrophil counts ($> 3.3\times10^9$ cells/L) and plasma creatinine level (> 62.5 µmol/L) were associated with VTE risk. Combination of these clinical and laboratory variables could be used for VTE risk evaluation in cancer patients.

3. In patients with pancreatic cancer, the doubling time (DT) of the tumor marker CA 19-9 predicted a VTE event, whereas CA 19-9 level per se was not associated with the risk of VTE. Patients with a CA 19-9 DT less than 4.4 months had a high risk of VTE, as half of them encountered a VTE event within 12 months. Such patients may benefit from individualized thromboprophylactic approaches.

4. A VTE after high-grade serous ovarian cancer (HGSOC) diagnosis was prognostic for reduced survival. Increased leukocyte and neutrophil counts and higher tumor marker CA 12-5 levels were associated with an increased risk of VTE, as was poor response to platinum-based cancer treatment. These clinical and laboratory variables should be integrated in VTE risk evaluation among HGSOC patients.

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It is finally done!

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