Biomarkers and Genetics for the Prediction of Venous Thromboembolism and Clinically Relevant Bleeding in Cancer Patients

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Abstract

Patients with cancer have a ninefold increased risk of venous thromboembolism (VTE) compared to the general population. Thromboprophylaxis with anticoagulants is the main primary prevention strategy to reduce VTE incidence in this high-risk population. However, the decision to prescribe thromboprophylaxis is complicated by the risk of anticoagulant-related clinically relevant bleeding, particularly in ambulatory cancer patients who may have variable bleeding risks that depend on cancer type, treatment regimen and comorbidities. Therefore, accurately identifying ambulatory cancer patients who will most likely to benefit from thromboprophylaxis – those at high risk of VTE but low risk of bleeding – is critical to maximize clinical benefit while minimize harm. Currently, VTE and bleeding risk scores in ambulatory cancer patients are suboptimal. Therefore, improved, individualized prediction tools are needed. The aim of this thesis is to address current evidence gaps and improve the prediction of VTE and clinically relevant bleeding risks in ambulatory cancer patients. The specific objectives of this thesis project are to: 1) summarize and investigate the association between genetic factors and VTE in cancer patients, 2) review the current evidence on biomarkers for VTE prediction in cancer patients, 3) evaluate the association and longitudinal changes of novel biomarkers with VTE and clinically relevant bleeding in cancer patients and, 4) train machine learning prediction models for both outcomes using biomarkers, genetic and clinical factors as predictors.

This thesis contains several components. The first chapter reviews the epidemiology of cancer-associated VTE and highlights the existing evidence gaps. The second and third chapters explored the associations between inherited thrombophilia and VTE in cancer patients. Briefly, in the studies described in these two Chapters, we found an increased VTE risk in cancer patients with non-O blood types, Factor V Leiden and Prothrombin Factor II G20210A compared to cancer

patients without these thrombophilias. In the fourth Chapter, we synthesized current evidence on blood-based biomarkers for VTE prediction, and identified nine promising biomarkers with predictive values varying based timing of measurement. In the study reported in Chapter 5, we investigated the associations between inflammatory and cardiac biomarkers with VTE and clinically relevant bleeding risk. The results of this study suggest a potential interplay between systemic inflammation, cardiac dysfunction and coagulation. In Chapter 6, the final study of this thesis, we trained machine learning models for the prediction of VTE and clinically relevant bleeding in ambulatory cancer patients using genetic, biomarker and clinical data. The concluding chapter discusses the key findings, strengths, limitations and implications of this doctoral research.

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List of Abbreviations

Abbreviation	Meaning
AIC	Akaike information criterion
ARI	Absolute risk increase
ARR	Absolute risk reduction
AUC	Area under the curve
BMI	Body mass index
CBC	Complete blood counts
CI	Confidence interval
CRNMB	Clinically relevant non-major bleeding
CRP	C-reactive protein
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
EV	Extracellular vesicles
FGG	Fibrinogen gamma gene
FVL	Factor V Leiden
F2 or FII	Factor II
F5 or FV	Factor 5
F11 or FXI	Factor 11
F13 or FXIII	Factor 13
GDF-15	Growth differentiation factor-15

GRADE	Grading of recommendations assessment, development and evaluation
HR	Hazard ratio
HWE	Hardy-Weinberg equilibrium
hs-TnT	high-sensitivity troponin T
IL-6	Interleukin-6
IQR	Interquartile range
LMWH	Low molecular weight heparin
MB	Major bleeding
MM	Multiple myeloma
MTHFR	Methylenetetrahydrofolate reductase
NLR	Neutrophil lymphocyte ratio
NNH	Number needed to harm
NNT	Number needed to treat
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OR	Odds ratio
PAI-1	Plasminogen activator inhibitor-1
PE	Pulmonary embolism
PY	person-years
QoL	Quality of life
QUIPS	Quality in prognostic studies
RCT	Randomized controlled trial

ROB	Risk of bias
ROC	Receiver operating characteristic
RR	Relative risk
SD	Standard deviation
SERPINA10	Serpin family A member 10
SHAP	Shapley additive explanations
SHR	Subdistribution hazard ratio
TACC	Treatment arm continuity correction
UFH	Unfractionated heparin
VEGF	Vascular endothelial growth factor
VEGFA	Vascular endothelial growth factor A
VTE	Venous thromboembolism
VWF	Von Willebrand factor

Chapter 1

Introduction

Venous thromboembolism (VTE) is a common and potentially life-threatening disease, with an estimated lifetime risk of approximately 8-10% in the general population[1,2]. It refers either to the formation of a blood clot within a deep vein, which is designated as deep vein thrombosis (DVT) or the situation in which the clot travels to the lungs, called pulmonary embolism (PE). The latter can cause death and morbidity, the former significant morbidity. VTE is commonly considered to be a multifactorial condition provoked by multiple causal and interacting risk factors. Based on the Rothman causal model[3], risk factors for VTE are thus predominantly neither necessary nor sufficient component causes for VTE. Instead, the development of a VTE involves the joint action of a multitude of component causes or risk factors. One important risk factor contributing to an increased risk of VTE is cancer and VTE events occurring as a complication of cancer are referred as cancer-associated VTEs.

1.1 Epidemiology of Cancer-Associated VTE

Cancer is a major risk factor for VTE. Patients with cancer have a ninefold increased risk of VTE compared to the general population and overall, cancer is a leading cause of VTE, accounting for approximately 20% of all VTE cases.[4,5] In cancer patients, the risk of VTE is highest within the first year following diagnosis, declines in years two and three, but remains elevated as long as the cancer exists.[6] However, the majority of VTE events occur within the first 6-months after diagnosis.[7] The increased risk of VTE during the beginning stages of cancer is likely related to the hypercoagulability from active cancer and the prevalent use of anti-cancer therapies and their procoagulant effects.

While the general population statistic of 8-10% reflects lifetime cumulative risk of VTE, the figures reported in cancer populations typically represent short-term or annual incidence. For instance, population-based data have shown that the annual incidence of VTE in patients with cancer increased from approximately 1% in 1997 to 3.4% in 2017.[5] This increase has been attributed to improvements in anti-cancer therapies and thus longer life expectancy and increased use of diagnostic imaging modalities.[5] With the existing continued efforts to improving cancer

outcomes, and the expected increase in yearly new cancer cases as a result of population growth and aging,[8] there is no doubt that we can expect the incidence of cancer-associated VTE to continue to rise. This presents a serious problem as VTE is associated with a high risk of mortality, morbidity, poor quality of life (QoL), may interfere with planned anti-cancer therapy regimens and increases the cost of healthcare due to increased use of healthcare resources.[9–13] Specifically, VTE development in patients with cancer is associated with a 3.4- to 6-fold increased risk of mortality[9,10], worse QoL scores in four different QoL questionnaires[13], chemotherapy omission and treatment delays[14], 50% to 86% higher healthcare costs[7,15,16], nearly threefold as many hospitalizations and days spent in hospital[7], and 1.5 times as many outpatient claims[7] (in the American healthcare system) compared to cancer patients without VTE. Altogether, the existing evidence and epidemiology of cancer-associated VTE provides a strong case in the importance of identifying those at high risk of VTE and implementing primary prevention strategies in these patients.

1.2 Prevention of VTE in Cancer

Primary prevention refers to "an action taken to prevent the development of a disease in a patient who is well and does not have the disease in question"[17]. According to Geoffrey Rose (1985)[18], there are two complementary approaches to primary prevention: the population approach and the high-risk approach. A population primary prevention approach aims to broadly shift and lower the risk of disease in the population as a whole, whereas a high-risk primary prevention approach aims to lower the risk of disease in high-risk individuals only. In the case of patients with cancer, a high-risk primary prevention approach for VTE is generally preferred. This is because the overall prevalence of VTE in non-selected cancer patients is not high (approximately 3% as noted above) that the potential risks of treatment (bleeding) may outweigh the potential benefit (VTE prevention). Furthermore, since cancer-associated VTE is influenced by non-modifiable risk factors (e.g., age, cancer type, cancer stage, anticancer treatments, etc.) identifying those in whom the risk-benefit ratio of prophylactic therapy is favourable is imperative. As a result, primary prevention strategies should be tailored to high-risk individuals who are more likely to benefit the most. **Table 1** summarizes the differing primary prevention strategies recommended in the current guidelines. Regardless of the setting, the use of preventative measures (either mechanically using mechanical methods [e.g., compression stockings] or pharmacologically

using anticoagulants) to prevent the development of VTE are referred to as thromboprophylaxis. The two main types of anticoagulants typically used for thromboprophylaxis include direct oral anticoagulants (DOACs) (e.g., apixaban, rivaroxaban) and parenteral anticoagulants (e.g., usually low molecular weight heparin [LMWH], but occasionally unfractionated heparin [UFH], fondaparinux). Parenteral anticoagulants, although fast-acting and do not require monitoring, are administered via injection, either subcutaneously or intravenously. This method of delivery can cause discomfort, reduce patient compliance and often requires the involvement of a healthcare provider[19,20] In contrast, DOACs are taken orally, are also fast-acting and do not require routine monitoring, offering a more convenient option for many patients.

Table 1. Primary prevention strategies for cancer patients based on guidelines

Setting	**General Guidelines Recommendation**	**Evidence**
Surgically-treated cancer patients	○ pharmacological thromboprophylaxis with LMWH, UFH or fondaparinux in patients undergoing major surgery at a low risk of bleeding for 10 days post-operatively[21–24] ○ In cases involving major abdominal or pelvic surgery, extended thromboprophylaxis is advised unless contraindicated.[21–25]	○ Reduced rates of VTE in surgically-treated cancer patients receiving pharmacological thromboprophylaxis[26,27] ○ Reduced rates of VTE in patients undergoing abdominopelvic cancer surgery with extended LMWH thromboprophylaxis[28]
Hospitalized cancer patients	○ In hospitalized cancer patients who are not actively bleeding and have no contraindications to anticoagulation, guidelines recommend thromboprophylaxis with LMWH, UFH or fondaparinux[21–24,29]	○ Reduced incidence of VTE in medically ill or hospitalized patients, including those with cancer, receiving thromboprophylaxis[30–32]

Ambulatory cancer patients receiving systemic therapy	○ thromboprophylaxis with apixaban, rivaroxaban or LMWH in higher risk patients for a duration of up to 6-months.[21–25,33]	○ Reduced rates of VTE in ambulatory cancer patients receiving anticoagulation.[34–38] ○ Targeted prophylaxis in high-risk patients (identified using the Khorana score) reduced VTE incidence[34,35]

1.3 Clinical Dilemma and Current Risk Assessment Models

While the thromboprophylaxis recommendations in surgically-treated and hospitalized cancer patients are generally widely accepted in clinical practice, it is not the same for ambulatory cancer patients receiving systemic therapy. Studies have shown that VTE risk assessment using the Khorana score – a validated clinical prediction tool that assigns points based on five variables including cancer type, body mass index, and baseline blood counts[39] – and the use of thromboprophylaxis in this population remain underused by clinicians[40,41], contrary to existing guidelines. This low adherence may stem from factors such as clinicians' uncertainty about the clinical benefit of thromboprophylaxis in this population, concerns about the risk of bleeding complications and challenges in effectively assessing VTE risk in ambulatory cancer patients. **Figure 2** outlines the risk and benefits of using thromboprophylaxis in high-risk ambulatory cancer patients receiving systemic therapy. Particularly, ambulatory cancer patients with an intermediate- to high-risk Khorana score (i.e., ≥ 2) are estimated to have an VTE incidence rate of 9-10%.[5,34,35] Whether this incidence rate is high enough to justify routine thromboprophylaxis in this population remains a topic of debate. Additionally, the non-negligible potential risk of anticoagulant-related bleeding events,[42] which can increase the risk of mortality[43,44] and outweigh the benefits of preventing VTE, may further discourage clinicians from prescribing thromboprophylaxis in ambulatory cancer patients. This is supported by the numbers needed to treated (NNT) of 17 and 36 to prevent one VTE event versus numbers needed to harm (NNH) of 29 and 59 for the combined risk of major bleeding and clinically relevant non-major bleeding

(CRNMB) from the two trials evaluating thromboprophylaxis with DOACs compared to placebo - the AVERT and CASSINI trials, respectively[34,35]. In other words, for every 100 patients treated, approximately four VTE events would be prevented but this comes at the cost of two patients experiencing a bleeding event, highlighting the difficult balance between preventing VTE and avoiding harm from bleeding complications. Moreover, the Khorana score's limited predictive accuracy may also contribute to its underuse. In the derivation and validation cohorts of the Khorana score[39], the results show that many patients who experienced a VTE are not classified as high-risk (64.3%) and many patients classified as high-risk did not develop a VTE (93.3%). External validation studies have also reported c-statistics ranging from 0.50 to 0.70 [45–59] with sensitivities ranging from 60% to 91% and PPV's from 19% to 36% at thresholds of ≥ 3 or ≥ 2[53,56–60], indicating suboptimal performance and leaving room for improvement. Other risk assessment models have been developed. The Vienna CATS Score, Protecht Score and Conko Score are modified versions of the Khorana score, which utilizes other predictors to help discriminate between high- and low-risk patients.[61–63] Although these modified scores were developed in hopes of improving VTE prediction, their discriminatory performance in external validation studies were also suboptimal. The vast majority of the c-statistics for these scores were between 0.50 to 0.70[49–51,53,54] , which suggests that these scores may perform only marginally better than random chance and may not be more effective than the Khorana score. The COMPASS-CAT score focuses more on cancer-related predictors and patient comorbidity[64] while the CATS/MICA score is a simple model with only two factors, D-dimer and tumor site[65]. In external validation studies, the c-statistics for these scores varied from 0.62 to 0.91 in three studies[51,55] and 0.66 to 0.68 in two studies[52,65], respectively. Importantly, the TiC-Onco and ONCOTHROMB scores were derived taking into account both genetic and clinical risk factors.[58,59] They have performed significantly better than the Khorana score in identifying high-risk patients for VTE in their derivation cohorts[58,59] but these scores have not undergone extensive external validation. Nonetheless, these findings provide proof-of-concept that including genetic risk factors in risk assessment models may improve VTE risk prediction. There is a growing consensus that improving VTE risk prediction in ambulatory cancer patients is warranted to more precisely identify high-risk patients who are most likely to benefit from thromboprophylaxis.

Similarly, incorporating an accurate and reliable bleeding risk model could further support decision-making concerning thromboprophylaxis and optimize patient outcomes. Five of the existing bleeding scores mainly derived in other patient populations (i.e., anticoagulated patients with atrial fibrillation, VTE or cancer-associated VTE) have been externally validated in patients with cancer in the primary care setting, likely to include ambulatory patients, and the results showed that none of the scores could accurately predict bleeding.[66] Thus, there is a need to further refine and develop bleeding risk assessment tools tailored specifically for ambulatory cancer patients to ensure better prediction and management of both thrombotic and hemorrhagic risks.

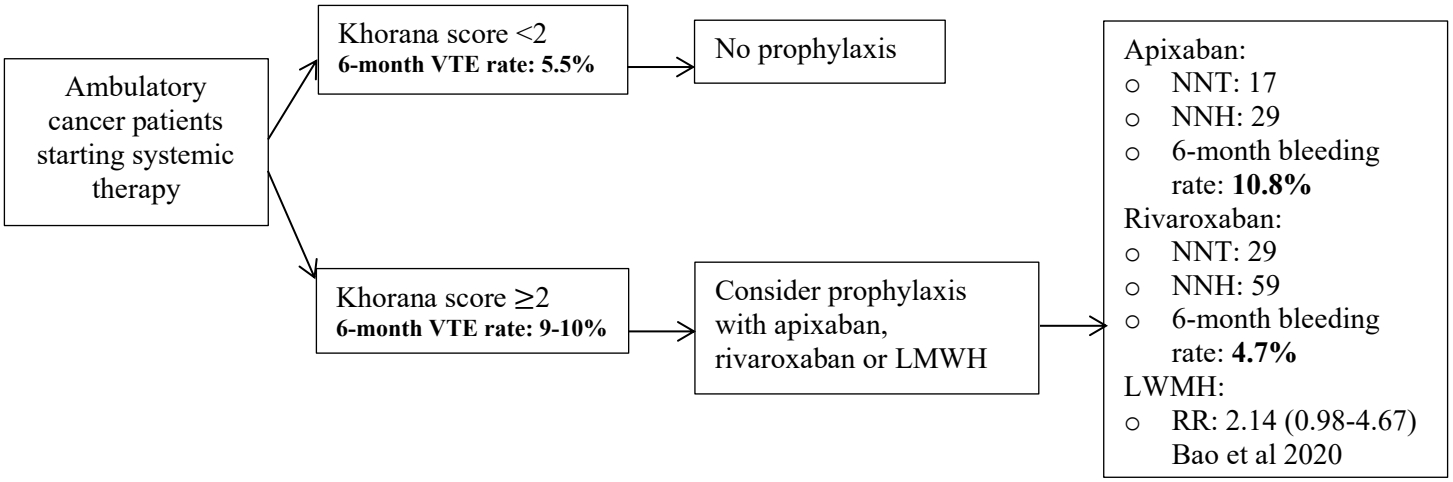

Figure 1. Summary of the clinical dilemma regarding the benefit (prevention of VTE) versus harm (risk of bleeding) of administering thromboprophylaxis to "high-risk" ambulatory cancer patients

1.4 Risk Factors for Cancer-Associated VTE

While the overall VTE risk is increased in patients with cancer, the risk of VTE varies significantly due to a range of other patient-related, cancer-related and treatment-related risk factors. Table 1 provides a summary of the existing evidence-based risk factors for cancer-associated VTE. Although this list is not exhaustive, it highlights the most researched risk factors for VTE in larger cohorts of cancer patients.

Table 2. Risk factors for cancer-associated VTE

Patient-related (Acquired)	Patient-related (Inherited)	Cancer-related	Treatment-related
○ Older age[5,67,68] ○ Obesity[7,69,70] ○ Prior VTE[5,69,71–74] ○ Family history of VTE[72,75] ○ Renal disease[76] ○ Infection[68,70] ○ Thrombocytosis[73] ○ Immobility/ hospitalization[70,71,74]	○ Ethnicity[69,77] ○ Inherited thrombophilia: FVL[78–83], FGG[80], Non-O blood type[84–86]	○ Primary cancer type: Pancreatic[5–7,69,87] Gastric[7], Gastrointestinal[87,88], Lung[7,87–89], Brain[69,87], Acute lymphoblastic leukemia[69], Hodgkin and non-Hodgkin lymphoma[5], Ovarian[5,87] or gynecologic[89], Bone[87], Sarcoma[89], Myeloma[89], Prostate[89] and hematologic malignancies[87] ○ Cancer stage[5,6,69,70,74,81,87,90] ○ Central venous catheter use[70]	○ Chemotherapy use[5,6,69,70,72,87] ○ Radiotherapy[5] ○ Surgery[5,91] ○ Targeted therapy[5,69] ○ Immunotherapy[5,69]

1.5 Biomarkers of Cancer-Associated VTE and Hemostasis

According to the pathophysiology of cancer-associated VTE, the prothrombotic effects of cancer and its treatment implicate a range of blood biomarkers. As such, it is not surprising that cancer patients who develop VTE exhibit different biomarker profiles compared to those who do not. For instance, research has demonstrated that cancer patients with VTE have higher levels of

tissue factor[92,93], microparticle tissue factor activity[92,94,95,96], plasminogen activator inhibitor-1 (PAI-1)[97], von Willebrand factor (VWF)[98] and soluble P-selectin[99] compared to those without VTE. Additionally, complete blood counts (CBC), particularly, platelet counts, white blood count and hemoglobin, have also been shown to be different in VTE vs non-VTE patients with cancer. Specifically, elevated platelet and white blood counts, as well as low hemoglobin, are associated with an increased VTE risk in cancer.[39,100,101] These components are important indicators of hypercoagulability and VTE since they reflect the overall hemostatic environment which may be altered by the cancer itself, inflammation or cancer treatments. Another common biomarker known to be higher in patients with cancer who develop VTE is D-dimer, a protein fragment released in the blood when a clot is degraded.[102,103]

Furthermore, cancer often induces systematic inflammation, which increases the levels of various pro-inflammatory cytokines subsequently triggering hypercoagulation. As such, biomarkers of inflammation, like C-reactive protein (CRP) and interleukins (e.g., interleukin-6), may provide additional insight into the underlying mechanisms of cancer-associated VTE. Elevated levels of these biomarkers have been shown to correlate with an increased risk of thrombosis in cancer[72,104–106], highlighting the crucial role of inflammation in modulating coagulation pathways in cancer patients. Growth differentiation factor-15 (GDF-15), another inflammatory cytokine, has emerged as a potential biomarker of VTE[107], but its role in predicting VTE specifically in cancer remains underexplored. Given its association with poor prognosis and bleeding[43,108,109], investigating GDF-15, in addition to other inflammatory biomarkers, could offer insights into the relationship between inflammation, coagulation and thrombotic risk in this population.

Similarly, cardiac biomarkers such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hs-TnT) have been associated with thrombotic and bleeding risk in non-cancer populations, including those with atrial fibrillation and heart failure. [110–114] While their relevance to VTE and bleeding risk in cancer patients remains unclear, elevated levels of NT-proBNP and hs-TnT may indicate a prothrombotic or pro-bleeding state, as they often reflect underlying cardiac conditions known to influence coagulation, such as atrial fibrillation[115–117], heart failure[118–121] and peripheral artherosclerotic disease[122,123]. Further research is needed to explore how these cardiac biomarkers interact with coagulation pathways in the context of cancer.

All in all, given the intertwined roles between systematic inflammation and cardiovascular stress in the pathogenesis of cancer-associated VTE, investigating inflammatory and cardiac biomarkers may enhance our ability to predict, diagnose and stratify VTE or bleeding risk in patients with cancer. Additionally, given the complex interplay between clinical, blood, and genetic biomarkers in cancer-associated VTE and bleeding, traditional risk scores may not fully capture the multidimensional nature of risk. Machine learning approaches offer the ability to integrate potentially non-linear and interacting variables, and may improve the predictive accuracy of VTE and bleeding risk tools in cancer patients, which remains to be explored further.

1.6 Thesis Objectives

In this thesis, the aim was to fill important evidence gaps relating to VTE and bleeding risk stratification in ambulatory patients with cancer, with the ultimate goal of improving prediction and management. The evidence gaps we addressed are summarized in **Figure 3**. Mainly, we aim 1) to summarize and investigate the association between genetic factors and VTE in cancer patients, 2) to summarize the current evidence on biomarkers for VTE prediction in cancer patients, 3) to evaluate the association and longitudinal changes between novel biomarkers with VTE and bleeding in ambulatory cancer patients, and 4) to develop VTE and bleeding risk machine learning models in ambulatory cancer patients.

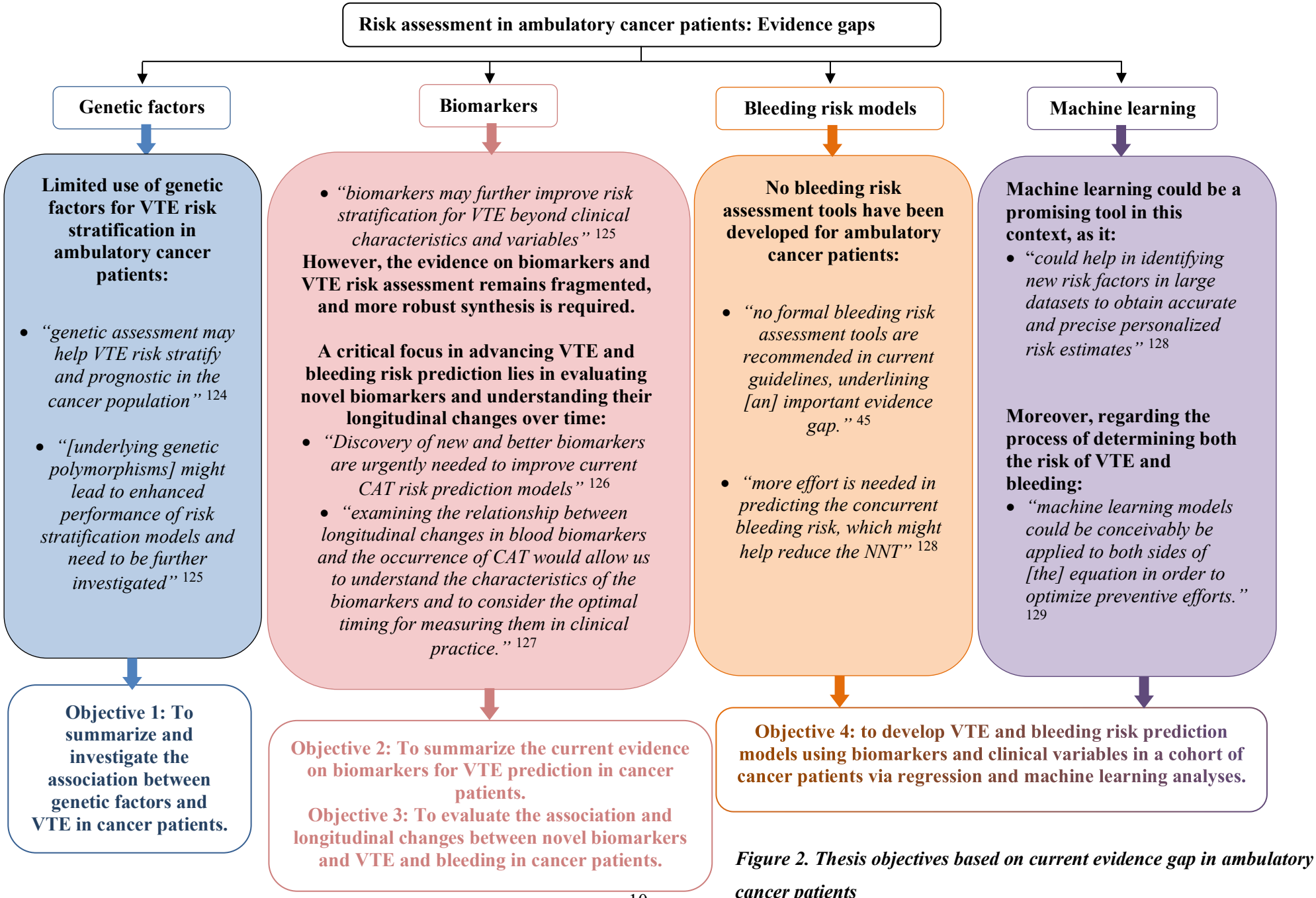

Figure 2. Thesis objectives based on current evidence gap in ambulatory cancer patients

1.7 Thesis Organization

This thesis is an article-based thesis formatted in accordance with the University of Ottawa School of Epidemiology and Public Health doctoral thesis guidelines. **Chapter 1** provides an introduction to the research topic, offering a comprehensive view of the background, key evidence gaps and rationale for this research. **Chapters 2 and 3** represent the first two articles of the thesis, aimed at investigating the association between genetic factors, also known as inherited thrombophilia, and VTE risk in cancer patients. **Chapter 4** is a systematic review and meta-analysis summarizing the current evidence on the associations between blood biomarkers and VTE risk in cancer patients. **Chapter 5** represents an analysis of novel and longitudinal biomarkers for the prediction of VTE and bleeding in cancer patients, and **Chapter 6** presents VTE and bleeding risk machine learning models in cancer patients. Finally, **Chapter 7** provides a discussion of key findings from Chapters 2 to 6, including the strengths and limitations and the clinical implications of this thesis.

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Chapter 2

Thrombophilia Gene Mutations Predict Venous Thromboembolism in Ambulatory Cancer Patients Receiving Chemotherapy

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Preface to Chapter 2

This Chapter evaluated the association between inherited thrombophilia, such as non-O blood types, Factor V Leiden and Prothrombin Factor II G20210A, and risk of venous thromboembolism (VTE) and clinically relevant bleeding in a cohort of cancer patients. While both cancer and inherited thrombophilia are independently associated with increased VTE risk, it remains controversial whether inherited thrombophilia mutations contribute meaningfully to VTE risk within the oncologic setting. Thus, we conducted a post-hoc analysis of patients from

the AVERT trial (a previous randomized controlled trial evaluating primary thromboprophylaxis use in cancer patients) to determine whether these genetic variants were associated with VTE or bleeding during the 7-month follow-up period. The benefit (VTE prevention) and potential harm (risk of bleeding) of anticoagulation use among cancer patients with specific inherited thrombophilia was also assessed. The findings offer insight into the potential utility of inherited thrombophilia for VTE risk stratification and inform ongoing discussion regarding primary thromboprophylaxis and inherited thrombophilia screening in cancer patients.

2.1 Abstract

Background: Inherited thrombophilia and cancer both independently increase the risk of venous thromboembolism (VTE). However, whether the increased VTE risk associated with inherited thrombophilia exists in cancer patients is less clear.

Objectives: Our objective was to determine the influence of inherited thrombophilia on VTE and bleeding risk in moderate-high risk ambulatory cancer patients receiving chemotherapy.

Methods: We conducted a post-hoc analysis using blood samples from patients enrolled in the AVERT trial to determine if previously recognized thrombophilia gene mutations (Prothrombin FII G20210A, Factor XI, Fibrinogen Gamma, Serpin Family A Member 10, Factor V K858R, Factor XIII, Factor V Leiden (FVL), and ABO blood) were associated with VTE or bleeding during the 7-months after starting chemotherapy. Logistic regression was used comparing heterozygous and homozygous mutations (combined) to wild type. VTE rates, bleeding rates and risk differences for mutations stratified by prophylactic anticoagulation use were calculated.

Results: Of the 447 patients, there were 39 VTE and 39 bleeding events. The odds of VTE were significantly increased with FVL mutation and non-O blood type [OR: 5.2 (95%CI:1.9-14.7) and 2.7 (95%CI:1.2-6.1), respectively]. The use of anticoagulation prophylaxis resulted in complete protection in FVL patients whereas those not receiving anticoagulation had a VTE rate of 119 per 100 patient-years. Lower VTE rates were also observed in non-O blood type patients taking prophylactic anticoagulation. No other thrombophilia genes tested were significantly associated with VTE or bleeding.

Conclusions: Our results indicate FVL mutation and ABO blood type may be important VTE predictors in cancer patients starting chemotherapy.

Keywords: Venous Thromboembolism, Neoplasms, Thrombophilia, Genes, Hemorrhage

2.2 Introduction

Inherited thrombophilia refers to genetic predisposition to venous thromboembolism (VTE).[1] These mutations are biologically linked with increased VTE risk due to their direct or indirect influence on coagulation proteins and factors. For example, two well-known inherited thrombophilia, the Factor V Leiden (FVL) and Prothrombin G20210A mutations, are characterized by high levels of thrombin and prothrombin, respectively.[2–4] In the general population, the prevalence of inherited thrombophilia has been identified in 21% -35% of patients with VTE.[5–8]

In addition to inherited thrombophilia as a risk factor for VTE, cancer is a well-recognized risk factor. The 12-month incidence of VTE is nine-fold higher in cancer patients compared to the general population[9] and represents a common complication contributing to higher morbidity and mortality.[10–12] Current guidelines suggest consideration of VTE prophylaxis in higher risk ambulatory cancer patients (Khorana score ≥2) supported by evidence from two large randomized controlled trials.[13,14] However, some have expressed reservations about adoption to clinical practice.[15]Therefore, efforts to identify the highest risk cancer patients remains a priority to determine which patients would benefit the most from thromboprophylaxis.

The role of inherited thrombophilia on the risk for cancer-associated VTE remains controversial. Previous studies have shown varying results from no association to a seven-fold increased risk of cancer-associated VTE related to inherited thrombophilia.[16–18] For this reason, the utility of diagnosing thrombophilia remains controversial and such testing is not part of standard clinical practice, urging the need for more evidence on the association between inherited thrombophilia and cancer-associated VTE. This study aims to evaluate the prevalence of common inherited thrombophilia gene mutations and their association with the risk of VTE in ambulatory intermediate-to-high risk patients (Khorana score ≥2) starting chemotherapy. Specifically, the inherited thrombophilia genes that were measured included: Prothrombin Factor II G20210A (F2), Factor XI (F11), Fibrinogen Gamma chain (FGG), Serpin Family A Member 10 (SERPINA10), Factor V K858R (F5), Factor XIII (F13), FVL and ABO genes. We chose these genes based on their positive association with VTE in the literature.[19,20] In addition, we assessed the association between inherited thrombophilia and bleeding events as well as the effect of prophylactic anticoagulation among those with thrombophilia gene mutations. We

hypothesized that those with inherited thrombophilia will have a higher risk of VTE and a lower risk of bleeding.

2.3 Methods

Study Design

We conducted a post-hoc analysis of the AVERT trial (Apixaban to Prevent Venous Thromboembolism in Patients with Cancer). The AVERT trial was a double-blinded randomized controlled trial assessing the efficacy and safety of apixaban compared to placebo in intermediate-to-high risk cancer patients.[13] Details on trial methodology and findings have been published previously.[13] For this post-hoc study, inherited thrombophilia was determined using baseline blood samples and occurrence of VTE or bleeding events was evaluated consecutively in patients with and without selected inherited thrombophilia. Baseline blood samples were available if patients provided a blood sample at their baseline visit and consented to having this sample used for future genetics-based research. Given that the AVERT trial recorded temporary or permanent anticoagulation discontinuations during the study follow-up period of 7 months (included one month follow-up after the 6-month treatment period), our anticoagulation stratified incidence rates were based on person-time at risk while taking apixaban and person-time at risk while not taking apixaban. In other words, patients randomized to the apixaban group contributed person-time at risk to the off-anticoagulation stratum when anticoagulation discontinuation occurred and/or when they were followed up from month 6 to 7.

Participants

Briefly, the AVERT trial enrolled patients with a newly diagnosed or progressive cancer. Patients had to be 18 years or older with a Khorana score of 2 or more and initiating a new course of chemotherapy. For this study, all patients enrolled in AVERT with available baseline blood samples were included.

Variables and outcomes

Patient demographics and characteristics including ethnicity, age, cancer type and sex were collected at the time of randomization. Data on concomitant antiplatelet or prophylactic anticoagulation use and discontinuation were collected during the trial follow-up visits. We used

this data to determine the number of days on and off prophylactic anticoagulation for each patient. The primary efficacy outcome was VTE, defined for this analysis as objectively confirmed symptomatic or incidentally detected thromboembolic events including proximal lower or upper limb deep vein thrombosis (DVT), pulmonary embolism (PE), splanchnic or cerebral vein thrombosis occurring between the time of randomization (index date) and 7-month follow-up. For this study, the primary safety outcome was the composite of major bleeding and clinically relevant non-major bleeding (CRNMB) using the International Society on Thrombosis and Haemostasis definitions.[21,22]All outcomes were adjudicated by a central adjudication committee unaware of study drug assignment.

The inherited thrombophilias assessed included: F2 (rs1799963), F11 (rs2036914), FGG (rs2066865), SERPINA10 (rs2232698), F5 (rs4524), F13 (rs5985), FVL (rs6025) and ABO (rs8176719). The thrombophilia gene mutations were identified using the Agena Bioscience iPlex method (Agena Bioscience, San Diego, CA, USA) according to the manufacturer's instructions (Supplemental Table 1).

Statistical Analysis

Demographics and antithrombotic drug usage between individuals with VTE and no VTE were assessed using descriptive statistics. The prevalence of the genes among those with VTE and no VTE are reported in Table 1. We evaluated for Hardy-Weinberg equilibrium by comparing observed and expected genotype frequencies using an exact test. Logistic regression was used to estimate odds ratios (OR) and 95% Confidence Intervals (CI) for the relationship between the thrombophilia gene mutations and VTE and bleeding outcomes. Exact logistic regression was utilized when data were too sparse to estimate OR and 95% CI using conventional logistic regression. Multivariate logistic regression was also used to assess the relationship between thrombophilia and VTE/bleeding events while adjusting for the potential confounding effect of ethnicity (Caucasian vs non-Caucasian). All events (VTE or bleeding) during the 7-month follow-up were included. In all analyses, we compared any mutations (including either heterozygous or homozygous mutations) to wild type using all conclusive/non-missing observations for each mutation. In the case of the ABO gene, we compared non-O blood types to O blood types. For each significant thrombophilia gene mutation, incidence rates of VTE and bleeding were calculated by dividing the number of events while on or off prophylactic

anticoagulation by the number of person years of follow-up on within each mutation stratum. Additionally, we calculated absolute risk differences in each stratum. Receiver Operating Characteristic (ROC) Curves and Area under the Curves (AUC) of the Khorana score and Khorana score plus FVL and ABO as predictors were computed to compare the classification of each score. We performed a sensitivity analysis assessing whether follow-up or competing risk of death influenced the results using the Fine and Gray subdistribution hazard model. A p-value below 0.05 was considered statistically significant. All calculations or statistical analyses were performed in SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA), R Core Team version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) or Excel version 16.7 (Microsoft Corporation, Redmond, Washington, USA).

2.4 Results

From the 574 AVERT trial participants, 447 patients (265 females) with a median age of 63 had baseline blood samples available and were included in this study (Figure 1). The median follow-up was 195 days. The baseline characteristics of the 127 participants without a blood sample for analysis were similar to those with blood samples (Supplemental Table 2). During the follow-up of 7-months, there were 39 VTE events (8.72%) including 25 DVT, 13 PE, and 1 DVT with PE. Additionally, there were 39 patients who experienced bleeding events which included 10 major bleeding events, 28 CRNMB and one patient who experienced both a major bleeding and CRNMB. Details on patient characteristics can be seen in Table 1. Compared to patients who did not experience a VTE, patients who experienced a VTE had a similar mean age, sex distribution and use of concomitant antiplatelet agents (Table 1). Consistent with the main findings of the AVERT trial, prophylactic apixaban use was associated with a reduced risk of VTE (Table 1). Among the 39 (8.72%) patients who suffered a VTE event, the prevalence of thrombophilia gene mutations were, F2: 2.56%, F11: 79.5%, FGG: 31.6%, SERPINA10: 0%, F5: 35.9%, F13: 44.7%, FVL: 15.4% and ABO: 79.5%, compared to F2: 1.96%, F11: 75.5%, FGG: 42.3%, SERPINA10: 0.75%, F5: 45.3%, F13: 43.5%, FVL: 3.44% and ABO: 58.9% in those who did not get a VTE (n=408, Table 1).

Among the thrombophilia mutations tested**,** two gene mutations were significantly associated with VTE risk. Particularly, after adjustment for ethnicity, the risk of VTE was significantly increased in patients with FVL mutation compared to those without the mutation

(adjusted OR: 5.24; 95% CI: 1.86-14.70; *p=0.0017*) and in patients with non-O blood type compared to those with O blood type (adjusted OR: 2.72; 95% CI: 1.22-6.08; *p=0.0144)* (Table 2). No other thrombophilia genes were significantly associated with the development of VTE (Table 2). F2 and SERPINA10 showed evidence of increasing risk of VTE however, these associations were not significant [OR: 1.36; 95% CI: 0.16- 11.20 and 2.57; 95% CI: 0-17.17, respectively] (Table 2). A sensitivity analysis using Fine and Gray models yielded similar results (Supplemental Table 3). When FVL and ABO were used as predictors in addition to the Khorana score, the AUC and ROC improved (Figure 2).

Moreover, the risk of bleeding was decreased in patients with F2, F5, FVL and the ABO gene mutation associated with non-O type blood by approximately 18%, 14%, 62% and 8%, and increased in patients with F11, FGG, SERPINA10 and F13 gene mutations by 54%, 76%, 173% and 29%, respectively, but none were statistically significant (Table 3). Similar results were observed when using Fine and Gray analysis (Supplemental Table 4).

To determine the efficacy and safety of prophylactic anticoagulation use in patients with FVL or non-O blood type, VTE and bleeding rates on and off prophylactic anticoagulation were calculated, as well as their absolute risk differences (Table 4). Among patients with FVL, the crude rate of VTE was 0 on prophylactic anticoagulation (0 events during 4.24 person-years of follow-up) and 119.48 (95% CI: 49.66-246.28) per 100 person-years (PY) off anticoagulation (6 events during 5.02 person-years of follow-up), resulting in a significant VTE absolute risk reduction (ARR) of 119.48 (95% CI: 23.88-215.08) attributed to prophylactic anticoagulation (Table 4). No bleeding events occurred in FVL patients while on or off prophylactic anticoagulation (Table 4). Among non-O blood type patients, the crude rate of VTE was 6.50 (95% CI: 1.80-17.33) per 100 PY on anticoagulation and 34.88 (95% CI: 23.68-49.68) per 100 PY off anticoagulation (Table 4). The crude rates of bleeding in these patients were 22.40 (95% CI: 11.50-39.74) per 100 PY on anticoagulation and 15.59 (95% CI: 8.73-25.90) per 100 PY off anticoagulation. A significant absolute risk reduction of VTE attributed to prophylactic anticoagulation in patients with non-O blood types was observed (ARR: 28.38; 95% CI: 13.52-43.24) meanwhile, there was no significant absolute risk increase (ARI) of bleeding (ARI: 6.82; 95% CI: -9.45-23.08) (Table 4).

2.5 Discussion

In this post-hoc analysis of the AVERT trial, we found that FVL mutation and non-O blood group were more prevalent in patients who developed VTE, such that the risk of VTE was 5.2 and 2.7-fold higher for cancer patients with a heterozygous or homozygous FVL mutation and non-O blood type, respectively. 30.0% of patients with FVL mutation developed VTE compared to 7.8% without FVL, while 11.5% of non-O blood type patients developed VTE versus 4.6% with O blood type. This higher VTE risk was associated with a lower risk of bleeding, albeit not statistically significant. Remarkably, prophylactic anticoagulation resulted in complete protection in FVL patients (while taking apixaban) whereas those not receiving prophylactic anticoagulation had a VTE rate of 119 per 100 patient-years of observation. All other thrombophilia gene mutations, including F2, F11, FGG, SERPINA10 and F5, were not significantly associated with the occurrence of VTE or bleeding events. Additionally, we found that prophylactic anticoagulation use in patients with FVL mutation or non-O blood type significantly reduced the risk of VTE without significantly increasing the risk of bleeding. To our knowledge, this is the first study to evaluate several thrombophilia genes in relation to both the occurrence of VTE and bleeding events and the efficacy and safety of prophylactic anticoagulation in cancer patients with thrombophilia gene mutations.

Our findings of increased VTE risk in cancer patients with FVL mutation or non-O blood type were consistent with previous reports. Particularly, in 2015 and 2020, two large cohort-based studies found that FVL mutation significantly increased the risk of VTE by approximately 2-fold in cancer patients and report a prevalence of FVL mutation of approximately 13-14% in those who developed a VTE, similar to our finding of 15.4%.[17,19] Other case-control studies evaluating the odds of VTE among cancer patients with FVL mutation compared to those without, have also reported ORs ranging from 2.2 to 8.1, which again closely aligns with our OR of 5.2.[16,18,23–25] Despite the similarities, the present work overcomes some of the limitations from these previous studies by using non-registry data, adjudicated VTE and bleeding events occurring after a confirmed cancer diagnosis, ethnicity-adjusted ORs and a larger sample size with narrower CIs. Previous research also supports our findings of increased VTE risk among those with non-O blood types. Specifically, studies showed that patients with pancreatic, bladder and glioblastoma cancers with non-O blood types had increased odds of VTE compared to O blood types.[26–28] A positive association between non-O blood type and VTE risk was also

observed in a more recent study including multiple cancer types, but this significant association was specific for VTE that occurred between month 3 and 24 of follow-up only. [29] There are known mechanisms of thrombosis related to FVL mutation and non-O blood types. Patients with FVL mutation have resistance to activated protein C, which causes inefficient cleavage of factor VIII by activated protein C, leading to a hypercoagulable state.[30,31] On the other hand, patients with non-O blood types have higher levels of Von Willebrand Factor and Factor VIII compared to O blood type, which could lead to an increased risk of thrombosis. [29,32–34]

F2, F11, FGG, SERPINA10, F5 and F13 are other mutations that had been reported as risk factors for VTE.[19,20,35–37] In our analysis, we observed an increased, yet insignificant OR for Prothrombin F2 G20210A, which could be related to the low prevalence of this mutation, leading to a lack of power. However, this is consistent with previous studies. Similarly, the F11 gene was not significantly associated with VTE risk, as evidenced by Skille et al.[19], even though previous studies have shown it to be an independent contributor to DVT risk in non-cancer patients.(37) These results suggest that the genetic influence of this thrombophilia on VTE risk may not be the same in the cancer population. As for the remaining genes, including FGG, SERPINA10, F5 K858R and F13, although some studies reported an association with VTE risk in cancer[19,20,35,36] we did not demonstrate statistically significant associations but the odds ratios were in the same direction. Particularly, the lower OR attributed to the F5 K858R mutation and its potential protective effect against VTE aligned with prior studies.[20,36] The SERPINA10 mutation showed higher odds of VTE, as in an earlier study[20] but with a wide CI. On the other hand, the F13 mutation had a OR of almost 1 and FGG showed a reduced VTE risk which was the opposite to findings by others.[19,20,35]

While inherited thrombophilia mutations are associated with an increased risk of VTE, the effects of inherited thrombophilia mutations on the risk of bleeding are less clear, especially in the cancer population. A recent study including non-cancer patients showed that patients with FVL and/or Prothrombin G20210A mutations were significantly less likely to experience a major bleeding or CRNMB event compared to those with both wild-type genes.[40] Similarly, another study revealed that O-blood type was more prevalent in those with bleeding events.[41] In this study, while some inherited thrombophilia gene mutations (FVL and ABO) were associated with an increased risk of VTE, we did not find a significant reduction in the risk of bleeding

associated with any of the mutations, which could be due to both the modest sample size and the small number of bleeding events. Future studies should assess the association between both VTE risk and bleeding events in patients with inherited thrombophilia.

Our study has important clinical implications. Currently, standard clinical guidelines do not recommend thrombophilia screening among cancer patients. However, they do recommend consideration of primary thromboprophylaxis in patients with significant risk factors for VTE as they are most likely to benefit from primary prevention therapy.[42–45] The findings of this study and others [17,19,29] suggest that FVL and non-O blood types may be considered as additional risk factors when deciding on the use of primary prophylaxis in cancer patients with a Khorana score of ≥ 2, especially given the benefit from prophylactic anticoagulation without an increased risk of bleeding found in this study.

Our study has limitations. First, the results of this study are limited to patients meeting the inclusion and exclusion criteria of the AVERT trial, including Khorana Score ≥ 2, not on anticoagulation for other indications, etc. and may not apply to all cancer patients. Second, residual confounding is possible as we were unable to adjust for the potential confounding effect of genetic ancestry and family history of VTE since these data were not collected. Similarly, the pooling of non-Caucasians as one group when adjusting for ethnicity in the analysis could have led to some loss of information. Unfortunately, given the sparsity of ethnic groups by outcome and thrombophilia, we were unable to adjust for individual ethnicity. Moreover, the sample size and the numbers of VTE and bleeding events were modest, which limited statistical power and resulted in wide CIs. In addition, there were relatively few cancer patients with FVL and the person-time follow-up was limited due to the design of the AVERT trial. In contrast, the strengths of this study include the inclusion of several inherited thrombophilia gene mutations and many types of cancers. Additionally, all outcome events were adjudicated by an independent committee and occurred after an objectively confirmed cancer diagnosis. Follow-up visits were conducted uniformly for each patient and the data were collected prospectively.

In conclusion, our study indicated that FVL mutation and non-O blood types are associated with an increased risk of VTE in intermediate to high-risk ambulatory cancer patients receiving chemotherapy and these patients benefited from prophylactic anticoagulation with a low risk of bleeding.

Ethics Approval: No ethics approval was sought for this analysis. The AVERT trial did receive ethical approval for plasma and DNA blood banking for future thrombosis research, on the condition of patient consent in accordance with the Declaration of Helsinski.

Contribution: D.R. designed the research, performed statistical analysis, analyzed results, created the tables, wrote the manuscript. T-F W., M.C., and P.W. designed the research, collected the data, interpreted the data and proofread the manuscript. R.M. and S.H. designed the research, assisted with performing the statistical analysis, analyzing the results and proofreading the manuscript. D.B. assisted with interpreting and analyzing the results, and proofreading the manuscript.

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Table 1. Distribution of baseline characteristics and thrombophilia gene mutations‡ in ambulatory cancer patients according to venous thromboembolism (VTE) events

Predictors		**VTE (n=447)**		**No. of Missing values**
		Yes (n=39)	**No (n=408)**	
Age, mean years (+/-SD)		62.13 (11.0)	61.26 (11.9)	
Sex, n male (%)		18 (46.15)	164 (40.20)	
Apixaban use, n (%)		14 (36.90)	207 (50.74)	
Antiplatelet use, n (%)		7 (17.95)	81 (19.85)	
Primary Type of Cancer	Brain	4 (10.26)	14 (3.43)	
	Breast	0	16 (3.92)	
	Colorectal	1 (2.56)	6 (1.47)	
	Gastrointestinal	6 (15.38)	32 (7.84)	
	Gynecological	9 (23.08)	116 (28.43)	
	Lung	0	44 (10.78)	
	Lymphoma	7 (17.95)	99 (24.26)	
	Myeloma	0	11 (2.70)	
	Pancreas	11 (28.21)	49 (12.01)	
	Other	1 (2.56)	21 (5.15)	
F2 gene, Prothrombin G20210A	Mutated	1 (2.56)	8 (1.96)	
	Wild type	38 (97.44)	400 (98.04)	
F11 gene	Mutated	31 (79.49)	308 (75.49)	
	Wild type	8 (20.51)	100 (24.51)	
FGG gene	Mutated	12 (31.58)	171 (42.33)	5
	Wild type	26 (68.42)	233 (57.67)	
SERPINA10 gene	Mutated	0	3 (0.75)	1
	Wild type	39 (100.00)	404 (99.26)	
F5 gene, K858R	Mutated	14 (35.90)	182 (45.34)	

	Wild type	25 (64.10)	223 (54.66)	
F13 gene	Mutated	17 (44.74)	177 (43.49)	2
	Wild type	21 (55.26)	230 (56.51)	
F5 gene, FVL	Mutated	6 (15.38)	14 (3.44)	1
	Wild type	33 (84.62)	393 (96.56)	
ABO gene	A, B or AB	31 (79.49)	239 (58.87)	2
	O	8 (20.51)	167 (41.13)	

Abbreviations: F2: Factor II, F11: Factor XI, F5: Factor 5, F13: Factor XIII, FVL: Factor V Leiden, FGG: Fibrinogen gamma chain, Serpin Family A Member 10 (SERPINA10), SD: standard deviation, VTE: Venous Thromboembolism

‡All thrombophilia gene mutations we tested were in Hardy-Weinberg equilibrium other than the ABO gene.

Table 2. Effect measures between thrombophilia gene mutations and venous thromboembolism (VTE) in ambulatory cancer patients

Predictors[1]	**Crude OR**	***P-value***	**Adjusted OR**[2]	***P-value***
F2 gene, Prothrombin G20210A	1.32 (0.16-10.80)	*0.7980*	*1.36 (0.16-11.20)*	*0.7779*
F11 gene	1.26 (0.56-2.83)	*0.5783*	*1.21 (0.53-2.72)*	*0.6531*
FGG gene	0.63 (0.31-1.28)	*0.2016*	*0.63 (0.31-1.29)*	*0.2105*
SERPINA10 gene	2.72 (0-18.13)	*0.7594*	*2.57 (0-17.17)*	*0.7486*[&]
F5 gene, K858R	0.68 (0.34-1.34)	*0.2593*	*0.67 (0.34-1.33)*	*0.2570*
F13 gene	1.05 (0.54-2.05)	*0.8821*	*1.01 (0.52-1.98)*	*0.9780*
F5 gene, FVL	5.10 (1.84-14.16)	*0.0017**	5.24 (1.86-14.70)	*0.0017**
ABO gene (ref=O)	2.71 (1.21-6.04)	*0.0149**	*2.72 (1.22-6.08)*	*0.0144**

Abbreviations: F2: Factor II, F11: Factor XI, F5: Factor V, F13: Factor XIII, FVL: Factor V Leiden, FGG: Fibrinogen gamma chain, OR: Odds Ratio, SERPINA10: Serpin Family A Member 10, VTE: Venous Thromboembolism

*Significant association ($p<0.05$)

[&]Results determined using exact logistic regression

[1] Reference category is wild type other than the ABO gene

[2]Adjusted for ethnicity (Caucasian vs non-Caucasian)

Table 3. Effects measures between thrombophilia gene mutations and bleeding events in ambulatory cancer patients

Predictors[1]	**Crude OR**	***P-value***	**Adjusted OR**[2]	***P-value***
F2 gene, Prothrombin G20210A	0.83 (0-4.18)	*0.4363*	*0.82 (0-4.12)*	*0.4327*[&]
F11 gene	1.50 (0.64-3.51)	*0.3457*	*1.54 (0.66-3.63)*	*0.3208*
FGG gene	1.74 (0.90-3.36)	*0.1017*	1.76 (0.91-3.40)	*0.0940*
SERPINA10 gene	2.72 (0-18.13)	*0.7594*	2.73 (0-18.26)	*0.7606*[&]
F5 gene, K858R	0.86 (0.44-1.67)	*0.6462*	*0.86 (0.44-1.67)*	*0.6495*
F13 gene	1.25 (0.65-2.42)	*0.5001*	1.29 (0.66-2.52)	*0.4519*
F5 gene, FVL	0.35 (0-1.67)	*0.1538*	*0.38 (0-1.78)*	*0.1705*[&]
ABO gene (ref=O)	0.93 (0.47-1.81)	*0.8201*	*0.92 (0.47-1.80)*	*0.8122*

Abbreviations: F2: Factor II, F11: Factor XI, F5: Factor V, F13: Factor XIII, FVL: Factor V Leiden, FGG: Fibrinogen gamma chain, OR: Odds Ratio, SERPINA10: Serpin Family A Member 10

[&]Results determined using exact logistic regression

[1] Reference category is wild type other than the ABO gene

[2]Adjusted for ethnicity (Caucasian vs non-Caucasian)

Table 4. Absolute risk and incidence rates of VTE and bleeding according to FVL mutation and ABO blood type during anticoagulation

Treatment	Mutation group	VTE		Bleeding	
		Rates, per 100 PY (95% CI)	Risk Reduction (95% CI)*	Rates, per 100 PY (95% CI)	Risk Increase (95% CI)*
On prophylactic Anticoagulation	FVL Mutated	0	119.48 (23.88-215.08)	0	0
	FVL Wild type	5.35 (1.79-12.73)	17.01 (7.33-26.70)	25.07 (15.39-38.77)	8.80 (-4.71-22.31)
	AB blood type	6.50 (1.80-17.33)	28.38 (13.52-43.24)	22.40 (11.50-39.74)	6.82 (-9.45-23.08)
	O blood type	3.05 (0.28-14.21)	9.99 (-1.37-21.34)	25.45 (12.00-48.02)	9.89 (-10.79-30.56)
Off prophylactic Anticoagulation	FVL Mutated	119.48 (49.66-246.28)	--	0	--
	FVL Wild type	22.36 (15.29-31.67)	--	16.27 (10.37-24.40)	--
	AB blood type	34.88 (23.68-49.68)	--	15.59 (8.73-25.90)	--
	O blood type	13.03 (5.81-25.59)	--	15.56 (7.34-29.37)	--

Abbreviations: 95% CI: 95% Confidence Interval, FVL: Factor V Leiden, VTE: Venous Thromboembolism

*Absolute risk reduction for VTE calculated as $rate_{\text{off anticoagulation}} - rate_{\text{on anticoagulation}}$ and Absolute risk increase for bleeding calculated as $rate_{\text{on anticoagulation}} - rate_{\text{off anticoagulation}}$

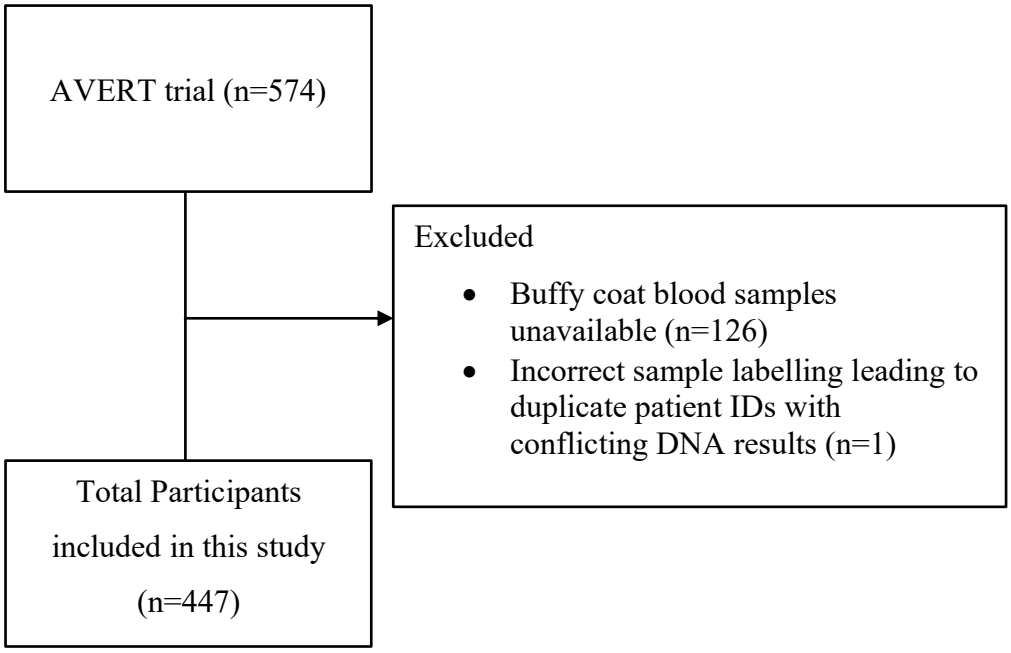

Figure 1. Thesis objectives based on current evidence gap in ambulatory cancer patients

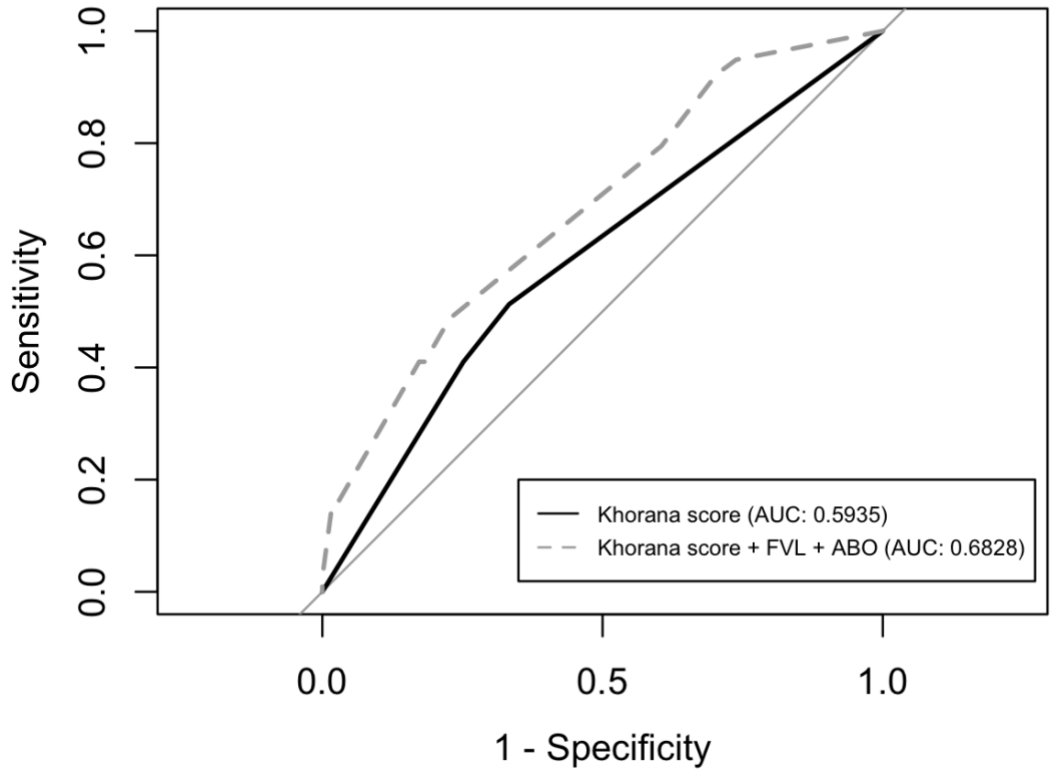

Figure 2. Receiving operating characteristic (ROC) curves comparing the Khorana score and Khorana score with added inherited thrombophilia predictors

2.7 Appendix

Supplemental Table 1. Thrombophilia gene mutation detection method used for the study

<table>
<tr><td>1. Multiplex PCR</td><td>A multiplex PCR was performed as follows:
20ng of template genomic DNA
5µL reaction mixture containing:
0.1µL (0.5 U) HotStar Taq enzyme (QIAGEN)
0.625µL of 10X HotStar Buffer
0.325µL of 25mM (total) MgCl2
0.25µL of 10mM dNTP mix
0.55µL of forward and reverse primer pool (1µM)
1.15µL of water.
The amplification cycles were performed as follows:<table><tr><td>Initial activation step:</td><td>15min</td><td>95℃</td></tr><tr><td>3-step cycling Denaturation:</td><td>20sec</td><td>95℃</td></tr><tr><td>Annealing</td><td>30sec</td><td>56℃</td></tr><tr><td>Extension</td><td>1min</td><td>72℃</td></tr><tr><td>Number of cycles</td><td>45 cycles</td><td></td></tr><tr><td>Final extension</td><td>3min</td><td>72℃</td></tr><tr><td>Hold</td><td></td><td>4℃</td></tr></table></td></tr>
<tr><td>2. Assessing Amplification</td><td>A few PCR reactions were run on QIAxcel (QIAGEN) to assess the amplification (1µL of PCR in 9µL of DNA Dilution Buffer (QIAGEN))</td></tr>
<tr><td>3. SAP Treatment</td><td>This is followed by a shrimp-alkaline-phosphatase treatment to deactivate the unused nucleotides which includes the following additions:
0.2µL of SAP Buffer
0.3µL of SAP
1.5µL of water
SAP cycling was 37℃ for 40min followed by 85℃ for 10min and a hold at 4℃.</td></tr>
<tr><td>4. Primer Extension</td><td>Next, a primer extension reaction (iPLEX Gold) was performed as follows:
0.94µL of extension primer mix
0.2µL of iPlex Terminator
0.2µL of iPlex Buffer
0.041µL of iPlex Thermo Sequenase
0.619µL of water.</td></tr>
<tr><td>5. Desalting</td><td>The products are desalted using 6mg of resin (Agena Bioscience).</td></tr>
<tr><td>6. Mass-spectrometry</td><td>Then, products were spotted on a 384-point SpectroCHIP (Agena Bioscience) using a nanodispenser. The distinct masses were determined by MALDI-TOF mass-spectrometry and data were analyzed using MassARRAY Typer Analyser software.</td></tr>
</table>

Supplemental Table 2. Distribution of baseline characteristics between participants and non-participants of post-hoc analysis

Predictors		**Non-Participants (n=127)**	**Participants (n=447)**
Age, mean years (+/-SD)		61.74 (12.06)	61.36 (11.85)
Sex, n male (%)		54 (42.86)	182 (40.72)
Apixaban use, n (%)		70 (55.56)	221 (49.44)
Antiplatelet use, n (%)		97 (76.38)	359 (80.31)
Primary type of cancer	Brain	6 (4.76)	18 (4.04)
	Breast	1 (0.79)	16 (3.59)
	Colorectal	6 (4.76)	7 (1.57)
	Gastrointestinal	10 (7.94)	38 (8.50)
	Gynecological	22 (17.46)	125 (27.96)
	Lung	15 (11.90)	44 (10.78)
	Lymphoma	38 (30.16)	106 (23.71)
	Myeloma	4 (3.17)	11 (2.46)
	Pancreas	18 (14.29)	60 (13.42)
	Other	6 (4.76)	22 (4.92)

Supplemental Table 3. Effect measures between thrombophilia gene mutations and venous thromboembolism (VTE) events in ambulatory cancer patients

Predictors[1]	**Crude SHR**	***P-value***	**Adjusted SHR**[2]	***P-value***
F2 gene, Prothrombin G20210A	1.45 (0.19-11.13)	*0.7233*	*1.50 (0.19-11.60)*	*0.6968*
F11 gene	1.36 (0.60-3.10)	*0.4646*	*1.30 (0.58-2.91)*	*0.5326*
FGG gene	0.69 (0.34-1.37)	*0.2858*	0.69 (0.34-1.37)	*0.2844*
SERPINA10 gene	NA		NA	
F5 gene, K858R	0.74 (0.38-1.43)	*0.3633*	*0.73 (0.38-1.42)*	*0.3587*
F13 gene	1.04 (0.54-2.00)	*0.9166*	1.01 (0.53-1.96)	*0.9686*
F5 gene, FVL	4.44 (1.88-10.49)	*0.0007**	4.26 (1.80-10.08)	*0.0010**
ABO gene (ref=O)	2.47 (1.14-5.36)	*0.0222**	*2.50 (1.15-5.41)*	*0.0204**

Abbreviations: F2: Factor II, F11: Factor XI, F5: Factor V, F13: Factor XIII, FVL: Factor V Leiden, FGG: Fibrinogen gamma chain, SERPINA10: Serpin Family A Member 10, SHR: Subdistribution Hazard Ratio, VTE: Venous thromboembolism

*Significant association ($p<0.05$)

[&]Results determined using exact logistic regression

[1] Reference category is wild type other than the ABO gene

[2]Adjusted for ethnicity (Caucasian vs non-Caucasian)

Supplemental Table 4. Effect measures between thrombophilia gene mutations and bleeding in ambulatory cancer patients

Predictors[1]	**Crude SHR**	***P-value***	**Adjusted SHR**[2]	***P-value***
F2 gene, Prothrombin G20210A	NA		*NA*	
F11 gene	2.02 (0.80-5.11)	*0.1385*	*2.07 (0.85-5.08)*	*0.1110*
FGG gene	1.86 (0.99-3.51)	*0.0550*	1.86 (0.99-3.51)	*0.0546*
SERPINA10 gene	NA		NA	
F5 gene, K858R	0.85 (0.45-1.61)	*0.6147*	*0.85 (0.45-1.61)*	*0.6170*
F13 gene	1.23 (0.66-2.31)	*0.5182*	1.26 (0.67-2.35)	*0.4728*
F5 gene, FVL	0.35 (0-1.67)	*0.1538*	*0.38 (0-1.78)*	*0.1705*[&]
ABO gene (ref=O)	0.93 (0.47-1.81)	*0.8201*	*0.92 (0.47-1.80)*	*0.8122*

Abbreviations: F2: Factor II, F11: Factor XI, F5: Factor V, F13: Factor XIII, FVL: Factor V Leiden, FGG: Fibrinogen gamma chain, OR: Odds Ratio, SERPINA10: Serpin Family A Member 10, SHR: Subdistribution Hazard Ratio

[&]Results determined using exact logistic regression

[1] Reference category is wild type other than the ABO gene

[2]Adjusted for ethnicity (Caucasian vs non-Caucasian)

Chapter 3

Inherited Thrombophilia Gene Mutations and Risk of Venous Thromboembolism in Patients with Cancer: A Systematic Review and Meta-Analysis

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Preface to Chapter 3

This Chapter presents a systematic review and meta-analysis examining the association between inherited thrombophilia and the risk of venous thromboembolism (VTE) in cancer patients with compared to cancer patients without inherited thrombophilia. Given that some inherited

thrombophilias such as, Factor V Leiden and Prothrombin Factor II G20210A, have a low prevalence, achieving a sufficiently powered study would require large patient cohorts and significant resources. To address this gap and enable more robust inferences, we synthesized the available evidence to compare VTE risk in cancer patients with versus without inherited thrombophilia to achieve sufficient power. In addition, we explored how differences in treatment setting, follow-up duration and outcome definitions may influence the potential associations. The findings offer a more comprehensive understanding of the potential role of inherited thrombophilia in cancer-associated thrombosis and may help guide future research and clinical decision-making regarding primary thromboprophylaxis and genetic testing in oncology.

3.1 Abstract

Background: In the general population, individuals with an inherited thrombophilia have a higher risk of thrombosis, but the effect of inherited thrombophilia on the risk of cancer-associated venous thromboembolism (VTE) remains controversial.

Objectives: Our objective was to determine the risk of VTE in cancer patients with inherited thrombophilia.

Methods: We conducted a systematic review and meta-analysis of studies reporting on VTE after a cancer diagnosis in adult patients who were tested for inherited thrombophilia. In September 2022, we searched Medline, EMBASE and Cochrane Central. Two reviewers screened the abstracts/full-texts and assessed study quality using the QUIPS tool. We used Mantel-Haenszel random-effects models to estimate pooled odds ratios (OR) of VTE and 95% confidence intervals (95%CI).

Results: We included 37 and 28 studies in the systematic review and meta-analysis, respectively. Most studies focused on specific cancer types and hematologic malignancies were rare. The risk of VTE was significantly higher in cancer patients with non-O (compared to O) blood types [OR: 1.56 (95%CI: 1.28-1.90)], Factor V Leiden (FVL) and Prothrombin Factor II G20210A mutations compared to wild types [OR: 2.28 (95%CI: 1.51-3.48) and 2.14 (95%CI: 1.14-4.03), respectively]. Additionally, heterozygous and homozygous Methylenetetrahydrofolate Reductase C677T had ORs of 1.50 (95%CI: 1.00-2.24) and 1.38 (95%CI: 0.87-2.22), respectively. Among those with Plasminogen-Activator Inhibitor-1 4G/5G, Vascular Endothelial Growth Factor (VEGF) A C634G and VEGF C2578A mutations, there was no significant association with VTE.

Conclusions: In conclusion, this meta-analysis provided evidence that non-O blood types, FVL and Prothrombin Factor II G20210A mutations are important genetic risk factors for VTE in cancer patients.

Keywords: genes, hemorrhage, neoplasms, thrombophilia, venous thromboembolism

3.2 Introduction

The risk of venous thromboembolism (VTE) is nine-fold higher in cancer patients compared to the general population[1] and represents a common complication contributing to elevated health care expenditures, morbidity and mortality in this population.[2–6] While malignancy itself correlates with hypercoagulability, the incidence of VTE varies based on individual patient, tumor and treatment-related factors. Amongst the risk factors, inherited thrombophilia is well-known for directly or indirectly influencing coagulation proteins or factors, causing a genetic predisposition to VTE. The two most common inherited thrombophilias in the Caucasian population are the Factor V Leiden (FVL) and the Prothrombin Factor II G20210A mutations. In the cancer population, the prevalence of these mutations range from 2.24%-8.46% and 2.05%-3.91% overall, which increases to 4.22%-38.46% and 2.56%-9.62% in cancer patients with VTE, respectively.[7–11]

Despite a higher prevalence of inherited thrombophilia among cancer patients with VTE, previous studies evaluating the association between inherited thrombophilia and VTE report varying results. Measures of association ranging from no association to moderate or large effect sizes have been reported,[12–14] causing controversy around the utility of determining the status of inherited thrombophilia in cancer. Currently, inherited thrombophilia screening among cancer patients is not part of standard clinical practice. However, current guidelines recommend consideration of primary thromboprophylaxis in high-risk patients,[15–18] which could include those with certain inherited thrombophilia. The lack of conclusive evidence urges the need for high-quality data on the association between inherited thrombophilia and cancer-associated VTE. Considering that most inherited thrombophilia (i.e., FVL and Prothrombin G20210A) are not common,[7–11] achieving a sufficiently powered study would require testing for inherited thrombophilia in a large number of patients at considerable cost. For these reasons, we conducted a systematic review and meta-analysis to investigate the association of inherited thrombophilia genes or gene mutations with the risk of developing cancer-associated VTE. We aimed to search all published observational and interventional studies to calculate odds ratios (OR) overall and in various subgroups of cancer patients.

3.3 Methods

This systematic review was conducted and reported in accordance to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) and updated Preferred Reporting Items for Systematic Reviews guidelines.[19,20] The protocol for this study has been published in the Open Science Framework Registry (https://doi.org/10.17605/OSF.IO/GQUKW) previous to starting the review. An a posteriori decision to split the results of the common pre-published protocol into two components (inherited thrombophilia and biomarkers) was made to ensure sufficient details are reported and to facilitate readability and interpretability.

Search Strategy

A systematic literature search was conducted in Medline (Ovid interface), EMBASE (Ovid interface) and Cochrane Central from inception to September 26th 2022. The overall search strategy included key terms relating to VTE, biomarkers, genetics and cancer (Supplemental Appendix 1). The references of included articles were also searched for studies that met eligibility criteria.

Eligibility Criteria

We included studies that adhered to the following inclusion criteria: 1) observational (cohort or case-control) or interventional study, 2) written in French, English, Chinese or Persian, 3) study patient population were human adult patients with cancer, 4) reported on the occurrence of first VTE, defined as objectively confirmed symptomatic or asymptomatic first VTE events including upper and lower limbs deep vein thrombosis (DVT), pulmonary embolism (PE) and splanchnic or cerebral vein thrombosis and 5) reported a measure of association (or ability to calculate) between thrombophilia genes/gene mutations and VTE such as Odds Ratio (OR), Hazard Ratio (HR) or Relative Risk (RR). Studies were included regardless of length of follow-up and method of gene/mutation measurement. The decision to include only inherited thrombophilia genes instead of all gene mutations was made a posteriori to reduce the high number of included studies with a narrower inclusion criteria and to remove the heterogenous tumor-specific gene mutations. We excluded studies that reported on leukemia or myeloproliferative neoplasms (MPN) because they might have specific malignancy related predisposition to certain VTE (such

as MPN associated splanchnic vein thrombosis), and do not reflect the general cancer population. In addition, prolonged thrombocytopenia and platelet dysfunction are common, which may confound outcomes. [21–23] This exclusion was not part of the original protocol.

Selection Process

Two reviewers independently screened the titles and abstracts of the articles using Covidence Systematic Review Software (Covidence, Melbourne, VIC, Australia). Consecutively, the full texts of all potentially eligible articles were independently screened by the reviewers. Any disagreement regarding the inclusion of an article was resolved via consensus or by a third reviewer. For full-text articles with missing data to determine eligibility, reviewers contacted, or attempted to contact, the corresponding author for clarification.

Studies that met the inclusion criteria were selected for data extraction. The data was collected using a pilot tested standardized electronic form. In our protocol, we prespecified that all data from articles meeting eligibility criteria would be collected independently by two reviewers. However, given the unexpected large quantity of data and studies included based on our protocol (n=138; 7 reporting on both biomarkers and genes, 102 reporting on biomarkers only and 29 reporting on genes only), one reviewer extracted the data of each included study and a second reviewer independently extracted the data of a random sample of the included articles (~20%). This allowed us to evaluate the accuracy of the data extraction of the primary data extractor by which we found approximately 92% agreement. We extracted the following data: study characteristics (e.g., title, authors, year of publication, setting), methodology (e.g. study design, eligibility criteria, length of follow-up), study population (e.g. sample size, age, sex, anticancer treatments), outcome (e.g. VTE definition), exposure of interest (e.g. gene or mutation, assay, method of measurement, risk alleles) and measures of association with confidence intervals or raw data (e.g. OR, HR, RR, 2x2 table). For studies with multiple reports, the data was extracted separately and the most recent report with the largest sample size was used when there were overlapping populations.

Risk of Bias Assessment:

Two independent reviewers assessed the risk of bias (ROB) of each included study using the Quality in Prognostic Studies (QUIPS) tool. The QUIPS tool contains six domains - participation, attrition, prognostic factor measurement, outcome measurement, confounding and statistical analysis and reporting - that need consideration when evaluating the validity and risk of bias in prognostic factor studies. Each domain was rated as high, moderate, low or unclear risk of bias and the overall risk of bias of each study was determined by rating of each domain, collectively. Raters also reviewed the studies for publication bias when more than 10 studies were included in the meta-analysis using funnel plots.

Data Synthesis:

Studies that reported a measure of association (or reported sufficient data to allow calculation) between gene/gene mutation and VTE occurrence were included. A meta-analysis of a specific gene/gene mutation was performed when two or more studies provided the necessary data (i.e., raw data or 2x2 table data). Due to the group size imbalances between the majority of the genes/mutations and event data, we used the Mantel-Haenszel random-effects model with treatment arm continuity correction (TACC) instead of the DerSimonian and Laird inverse variance random-effects model. However, as suggested in the article of Sweeting et al 2004[24], we performed sensitivity analyses using other pooling or continuity correction methods (i.e., Mantel Haenszel random effects model with 0.5 continuity correction added to zero cells, DerSimonian and Laird inverse variance random-effects model with TACC) to assess the impact of different assumptions. Additionally, sensitivity analyses were also performed to determine the influence of studies not in Hardy-Weinberg equilibrium (HWE). Heterogeneity among studies was assessed using the I^2 statistic. I^2 below 30% was considered as non-important heterogeneity; I^2 between 30% to 75% was considered moderate; and I^2 above 75% was considered considerable heterogeneity. The genes/gene mutations that could not be meta-analyzed were narratively summarized in a supplemental table. Subgroup and sensitivity analyses (when possible) were performed to investigate the potential differences in outcomes in certain patient populations. Particularly, we evaluated the effect of the genes/gene mutations in studies with a) different treatment settings (i.e., perioperative, other anticancer treatment), b) lengths of follow-up, c) VTE definitions (i.e., DVT-only, DVT and PE, DVT or PE with other unusual sites of VTE such as portal vein thrombosis, etc.) d) risk of bias and e) Hardy Weinberg equilibrium. We assessed

the certainty of evidence using the grading of recommendations assessment, development, and evaluation (GRADE) approach.[25] A *p* value of 0.05 or less was considered statistically significant and all analyses were performed using R version 4.2.3 (R Core Team and R Foundation for Statistical Computing, Vienna, Austria) and RStudio version 2023.06.1 (Posit software, PBC, Vienna, Austria).

3.4 Results

A total of 4274 studies were screened for eligibility, of which 3433 and 814 were excluded after title and abstract screening and full-text screening, respectively (Figure 1). Eventually, 37 studies[10–12,14,26–58] (27 studies identified via search strategy and 10 studies identified via reference list searching) involving different cancer types and treatments were included in the systematic review, of which 28 studies[10,11,14,26–30,32,33,37,38,40,42–53,55,57,59] were included in the meta-analysis (Supplemental Table 1). Key study characteristics and estimates are shown in Supplemental Tables 2 and 3. From the 28 studies included in the meta-analysis, 9 studies included various cancer types while the remaining 19 studies were in selected cancer types (3 lung, 3 multiple myeloma, 2 brain, 2 bladder, 2 breast, 2 gynecologic, 1 testicular, 1 lung or gastrointestinal, 1 pancreas, 1 colorectal and 1 breast or gastrointestinal). The majority of studies were cohort studies (11 prospective and 7 retrospective) while the other 10 were case-control studies. The studies were either conducted in surgical (n=6) or mixed treatment settings (n=30), which we analyzed jointly and separately with the use of subgroups because surgery is an additional risk factor for VTE and follow-up durations were shorter in these studies.

The ROB assessments for the QUIPS domains of each included study are summarized in Supplemental Figure 1. Many studies had overall moderate to high risk of bias due to confounding and bias due to study participation or outcome measurement. Bias due to study attrition could not be determined in the majority of studies due to missing information on patient eligibility and follow-up. The numbers of overall low, moderate and high risk of bias studies included in the meta-analyses of each gene are reported in Figure 2.

Twenty-nine thrombophilia genes or mutations were evaluated for VTE risk, however 22 were only evaluated in a single study and therefore, could not be meta-analyzed (Supplemental Table 1). The estimates and 95% confidence intervals (95% CI) of these genes or mutations are summarized in Supplemental Table 4. The seven thrombophilia genes or mutations that were

meta-analyzed include ABO blood type, FVL, Methylenetetrahydrofolate Reductase (MTHFR) C677T, Plasminogen-Activator Inhibitor-1 (PAI-1), Prothrombin Factor II G20210A, Vascular Endothelial Growth Factor (VEGF) C634G and Vascular Endothelial Growth Factor (VEGF) C2578A.

Seven studies reported on the association between non-O blood types and VTE.[27,28,50–52,55,57] In cancer patients with non-O blood types, the overall pooled OR for VTE was significantly increased [OR: 1.56 (95% CI: 1.28-1.90), $I^2 = 0\%$] compared to cancer patients with O blood type (Table 1). The odds were increased in both surgical and mixed treatment settings and remained increased irrespective of follow-up durations (Figure 3). Removal of the study that included screening-detected VTE[28] rather than only symptomatic events did not significantly change the pooled estimate (Figure 3). When the meta-analysis was restricted to studies with low risk of bias [n=5 (71%); Figure 2], the association between non-O blood group and VTE remained the same (Figure 3).

In the 18 and 13 studies evaluating FVL[10,11,14,27,29,32,33,38,40,42–46,48,49,53,59] and Prothrombin Factor II G20210[11,14,27,32,33,38,40,42,43,48,49,53,59] gene mutations, respectively, the overall odds of VTE were 2.28 (95% CI: 1.51-3.48, I^2=52%) and 2.14 (95% CI: 1.14-4.03, I^2=20%) in those with a gene mutation (Table 1). The pooled odds of VTE were increased in the post-surgical and mixed treatment settings for both mutations, although only statistically significant in the mixed treatment setting (Figure 3). Several studies did not specify the follow-up durations, which affected our ability to accurately perform a subgroup analysis by the length of follow-up (Figure 3). When the meta-analysis was restricted to studies that included VTE events with unusual sites of VTE (i.e., portal vein thrombosis), the association between FVL mutation and VTE increased while the association between Prothrombin Factor II G20210A mutation and VTE remained unchanged (Figure 3). The association between FVL mutation and VTE also remained similar when the meta-analysis was restricted to studies with low risk of bias whereas the association for Prothrombin Factor II G20210A mutation was similar but a wider 95% CI was observed (Figure 3). We found no publication bias according to the funnel plots for the analyses on FVL and Prothrombin Factor II G20210A gene mutations (Supplemental Figure 2).

In the remaining genes or mutations, we found that heterozygous and homozygous MTHFR C677T[14,26,33,49,53] were associated with pooled ORs for VTE of 1.50 (95%CI: 1.00-2.24) and 1.38 (95%CI: 0.87-2.22), respectively, but, only a heterozygous mutation was borderline

significant (Table 1). Among those with heterozygous and homozygous PAI-1 4G/5G[26,38,49,53], VEGFA C634G[30,47] and VEGF C2578A[30,37], no significant increase in the odds of VTE were found, but moderate to considerable heterogeneity was observed (Table 1).

Sensitivity analyses restricted to Mantel-Haenszel with 0.5 correction for zero cells, inverse variance weighting with TACC, removal of matched case-control studies, and removal of studies not in Hardy-Weinberg equilibrium yielded similar results (Supplemental Table 5, Figure 3, Supplemental Figure 3 & 4). Additionally, a sensitivity analysis limited to studies including only lower extremity DVT or PE as events revealed similar results for FVL and a higher OR for Prothrombin Factor II F20210A with a wider confidence interval (Supplemental Table 6).

3.5 Discussion

VTE is commonly regarded as a multicausal condition, driven by interactions between acquired and inherited risk factors. In the cancer population, large cohort studies have demonstrated that age, cancer type, metastasis, chemotherapy, surgery, radiotherapy, and patient history of VTE are the most commonly recognized cancer-associated VTE risk factors contributing to its pathogenesis. In this systematic review and meta-analysis investigating the role of inherited thrombophilia on the risk of cancer-associated thrombosis, our findings suggest that inherited thrombophilia including ABO blood type, FVL and Prothrombin FII G20210A mutations are also important risk factors contributing to thrombotic risk in cancer. By performing a meta-analysis, we found that cancer patients with a non-O blood type, FVL or Prothrombin FII G20210A mutation had a 1.56-, 2.28- and 2.14-fold increased risk of subsequent VTE compared to patients with O blood type or wild type genotypes, respectively. When a subgroup analysis (by treatment setting) was performed, the association between inherited thrombophilia and VTE risk was comparable for both surgical and mixed treatment settings.

The results that we observed are consistent with previous existing research. Our finding of increased VTE risk in patients with a non-O blood type was reported in three previous meta-analyses, one including all cancer studies (including pediatric and leukemia patients), and the others including various patient populations. In these meta-analyses, non-O blood type was significantly associated with VTE, with ORs ranging from 1.74 to 2.09,[60–62] thereby closely aligning with our OR of 1.56. The magnitude of our association is slightly smaller than the other studies, but the significant heterogeneity observed in the other two meta-analyses provides

evidence that the risk may vary in different patient populations. Prior research has attributed the increased risk of VTE in non-O blood types to higher levels of Von Willebrand Factor and Factor VIII level. The positive association between VTE risk and FVL and Prothrombin FII G20210A mutations was also reported in a meta-analysis conducted in the general population.[63] Additionally, we recently analyzed these three inherited thrombophilia genes in a cohort of 447 ambulatory cancer patients with a Khorana score ≥ 2.[64] Similar to our current study, we found that cancer patients with non-O blood type, FVL and Prothrombin FII G20210A mutations had an increased risk of subsequent VTE [adjusted ORs: 2.72 (1.22-6.08), 5.24 (1.86-14.70), 1.36 (0.16-11.20), respectively]. Certain effect measures of the study are larger compared to the results of this meta-analysis, which could be due to both the inclusion of higher risk patients (Khorana score ≥ 2) and the smaller sample size. When these results are included in our meta-analysis the updated pooled effect measures are 1.61 (1.23-1.96), 2.31 (1.58-3.39) and 2.08 (1.16-3.72) for ABO, FVL and Prothrombin FII G20210A, respectively.

Moreover, our findings related to the MTHFR C677T, PAI-1 4G/5G, VEGFA C634G and VEGF C2578A mutations also aligns with previous literature but were limited in the small sample size and significant heterogeneity. In this meta-analysis, we found a mildy increased risk of VTE in cancer patients with heterozygous MTHFR C677T mutation (but not homozygous). Given the small number of studies included, publication bias could not be assessed but was possible, and the small sample size limited the certainty of the point estimate. The finding of no association between the PAI-1 4G/5G mutation and VTE risk in cancer in this study, as in an earlier study,[66] suggests that the genetic influence of this thrombophilia on VTE risk is not relevant in cancer patients.

A subgroup analysis by treatment setting was performed in an attempt to estimate its influence on the association between inherited thrombophilia and VTE risk. We compared surgical vs mixed treatment settings on the basis that cancer surgery itself is a major risk factor for VTE, and since a prior study in colorectal cancer patients reported a higher overall 1-year incidence rate of VTE in surgical patients with thrombophilia mutations compared to without.[48] In our study, we found that studies recruiting only surgical patients had consistent ORs to studies with mixed treatment settings. But, for FVL and Prothrombin FII G20210A mutated patients, the ORs were only statistically significant in the mixed treatment settings, likely due to the small number of surgical studies, which resulted in a wide 95% CI. Nonetheless, the finding of

relatively similar ORs between surgical and mixed treatment setting studies is still an interesting finding given that follow-up durations were mostly short in the surgical studies (range: 1 - 11.1 months) compared to those with mixed treatment patients (range: 3 - 120 months).

Our meta-analysis provides clinical implications for cancer patients with inherited thrombophilia. Non-O blood type, FVL, and Prothrombin FII G20210A mutations may be risk factors to consider when assessing for VTE risk and deciding whether to use primary thromboprophylaxis. Although we could not analyze the results by anticoagulation use, in previous studies, a lower incidence of VTE was reported in patients with inherited thrombophilia during prophylactic anticoagulation use.[48,64] Remarkably, the evidence also suggests that the risk of bleeding may not be increased in non-O blood type and FVL mutated cancer patients taking prophylactic anticoagulation.[64] Other evidence also suggests that the combination of both clinical and genetic variables might better identify cancer patients at high risk of VTE.[64,68] However, currently, inherited thrombophilia screening is not part of standard clinical practice and is still a matter of debate. The cost-benefit and utility of inherited thrombophilia screening in cancer patients should be verified in future research. In particular, the impact of inherited thrombophilia screening on treatment decisions remains an important area of study.

There are some limitations to consider in our study. First, there were many inherited thrombophilia gene mutations that were only reported in one study or did not provide the necessary data for pooling, limiting our ability to meta-analyze results and make pooled inferences for these mutations. Second, ethnicity was commonly missing from included studies, preventing us from performing subgroup analyses by ethnicity. Similarly, the majority of studies did not control for ethnicity, family history of VTE or genetic ancestry, which could have led to residual confounding. Moreover, the included studies were commonly heterogenous in terms of patient characteristics and study design, which caused some heterogeneity in our pooled estimates and may limit generalizability to certain patient populations. Our study did not address the cost effectiveness and other potential implications of thrombophilia testing (such as implications on insurance, psychological anxiety, etc.) in patients with cancer, and whether testing for thrombophilia could influence the decision of thromboprophylaxis remains unclear.

In contrast, there are important strengths to our study. To our knowledge, this study is the first and largest meta-analysis to determine the risk of VTE in cancer patients with inherited thrombophilia. We included a large number of studies and participants yielding higher statistical

power than individual studies. Additionally, we performed different subgroup analyses which allowed us to explore potential differences in VTE risk in subgroups of cancer patients.

In conclusion, our meta-analysis confirmed that non-O blood type, FVL and Prothrombin FII G20210A mutations are risk factors for VTE in the cancer population. The findings may carry clinical implications and further studies are needed.

Contributions: DCR, TFW, RM and PW designed the research question. DCR, TFW, AZ, RM and PW designed the eligibility criteria and the screening strategy. DCR, TFW, RL, AZ, RM, PW and SH came up with the data extraction items. DCR, TFW, AZ, RM and PW developed the data synthesis strategy. DCR, TFW, AZ, RM and PW drafted the protocol manuscript, and it was reviewed and approved by all authors. DCR and RL extracted the data. DCR, RM, GZ and SH aided with data analysis. DCR and GZ completed the ROB assessments. DCR, TFW, RM, DB, SH and PW interpreted the results. All authors reviewed the results, proofread and approved the final version of the manuscript.

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Conflict of Interest: T-F. Wang reports advisory board honoraria from Servier and Valeo in addition to research funding from Leo Pharma. D. Roy, R. Lun, R. Mallick, D. Burger, G. Zitikyte, S. Hawken and P. Wells have no conflicts of interest to declare.

Ethics Approval: None.

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Table 1. Risk of venous thromboembolism (VTE) in cancer patients with inherited thrombophilia compared to those without

Thrombophilia Gene/Mutation	**N of studies**	**Mutated**		**Wild**		**I^2 (%)**	**Pooled OR (95% CI)**	***P-value***	**Certainty of evidence (GRADE)[&]**
		VTE	**Total**	**VTE**	**Total**				
ABO blood type	7	362	2759	165	1960	0	1.56 (1.28-1.90)	*<0.001*	⊕⊕⊕⊕ **High**
Factor V Leiden	18	218	701	1226	7707	51.7	2.28 (1.51-3.48)	*<0.001*	⊕⊕⊕⊖ **Moderate** Due to risk of bias[1]
MTHFR C677T (heterozygous) MTHFR T677T (homozygous)	5	146 50	300 98	190	441	34 0	1.50 (1.00-2.24) 1.38 (0.87-2.22)	*0.0473* *0.1756*	⊕⊕⊖⊖ **Low** Due to risk of bias and imprecision[1,2]
PAI-1 4G/5G (heterozygous) PAI-1 4G/4G (homozygous)	4	128 70	416 199	111	281	8.2 46.0	0.93 (0.61-1.40) 1.46 (0.65-3.29)	*0.7125* *0.3582*	⊕⊕⊖⊖ **Low** Due to risk of bias and imprecision[1,2]
Prothrombin FII G20210A	13	55	102	937	2872	20.5	2.14 (1.14-4.03)	*0.0179*	⊕⊕⊕⊖ **Moderate** Due to risk of bias[1]
VEGFA C634G (heterozygous) VEGFA C634C (homozygous)	2	22 4	194 54	11	141	60 58.6	1.25 (0.31-4.99) 1.18 (0.15-9.52)	*0.7553* *0.8787*	⊖⊖⊖⊖ **Very Low** Due to risk of bias, imprecision and inconsistency[1,2,3]

VEGF C2578A (heterozygous) VEGF C2578C (homozygous)	2	23 14	202 127	10	79	79.8 77.3	2.29 (0.02-275.8) 2.01 (0.04-108.3)	*0.7345* *0.7312*	⊖⊖⊖⊖ **Very Low** Due to risk of bias, imprecision and inconsistency[1,2,3]

Abbreviations: MTHFR=Methylenetetrahydrofolate reductase, OR=Odds Ratio, PAI-1=Plasminogen-activator inhibitor-1, VEGF=Vascular endothelial growth factor, VEGF=Vascular endothelial growth factor A

[&]High certainty of evidence is represented by four positive symbols (⊕⊕⊕⊕) but, for each downgrade in certainty, a positive symbol (⊕) was changed to a negative symbol (⊖)

[1] Half or the majority of studies had a moderate-high risk of bias

[2] Low event rates with small sample size

[3] The I^2 is large, suggesting that there is high heterogeneity between the two studies

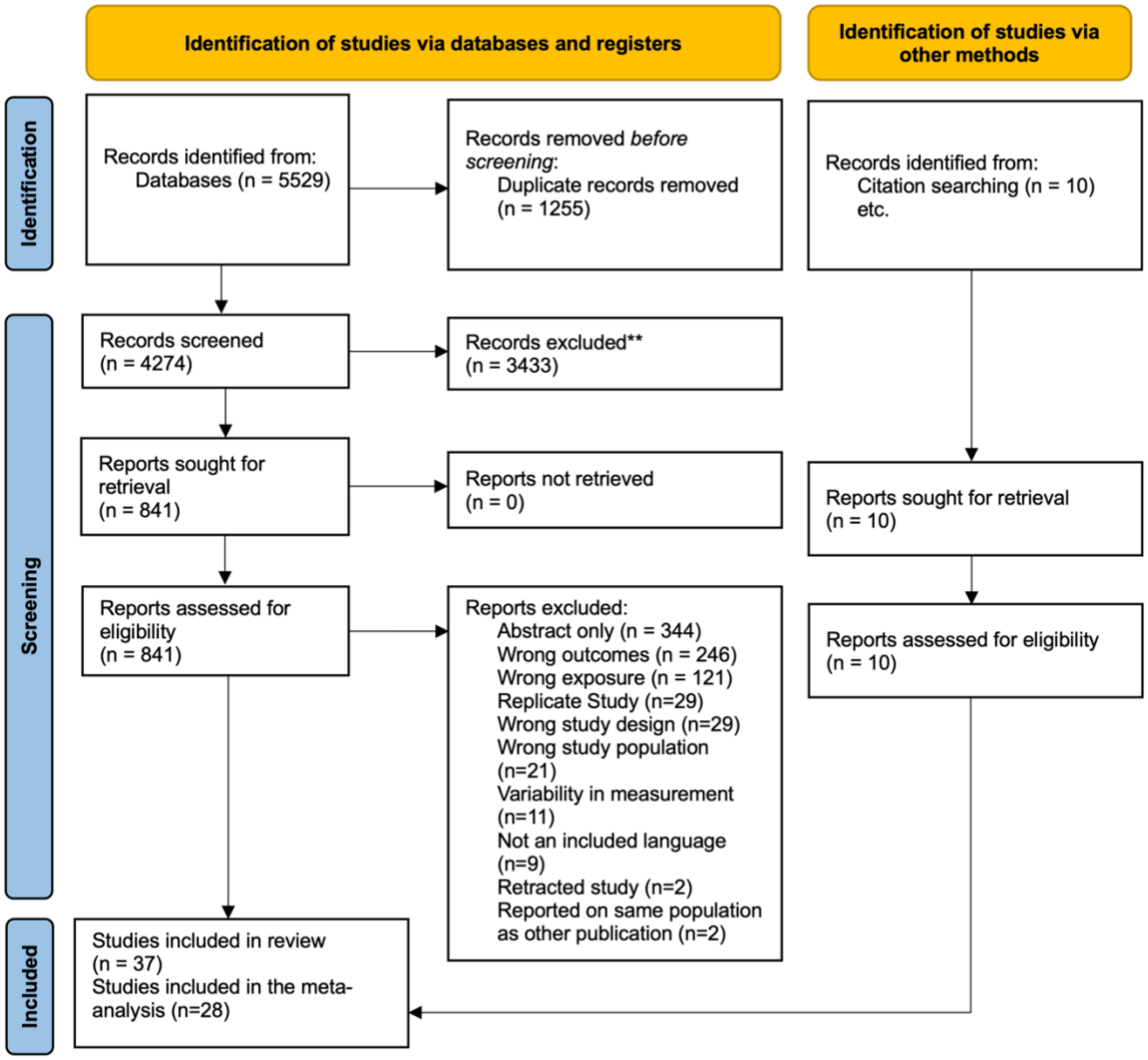


Figure 1. PRISMA flow diagram of search for studies meeting inclusion criteria

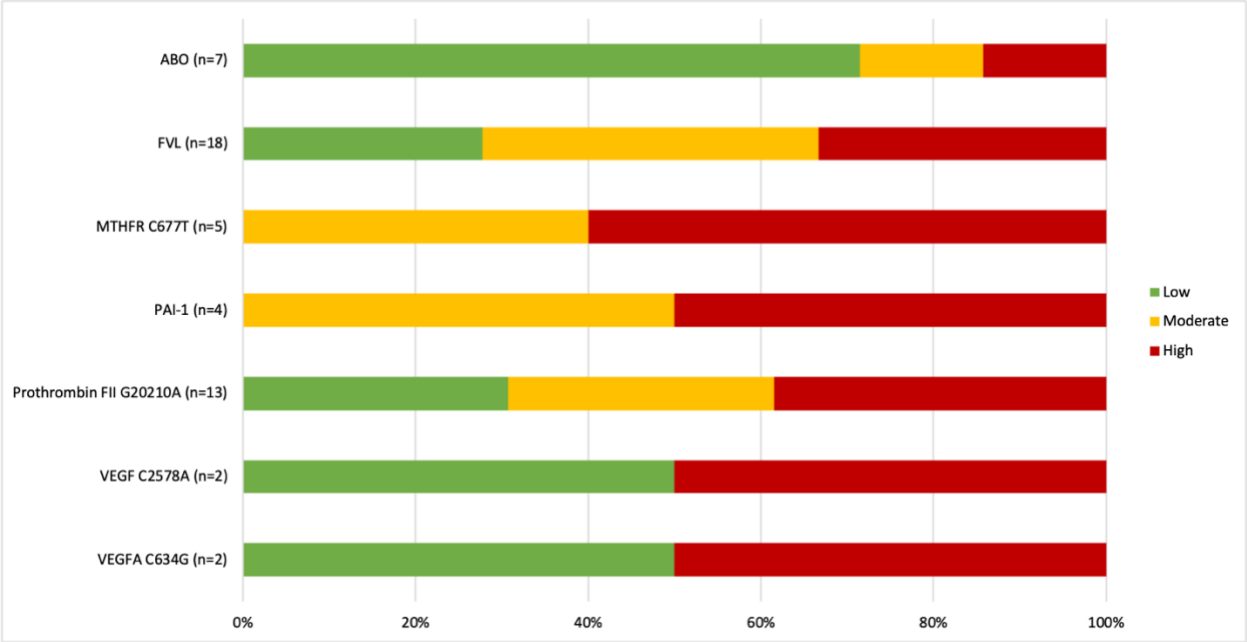
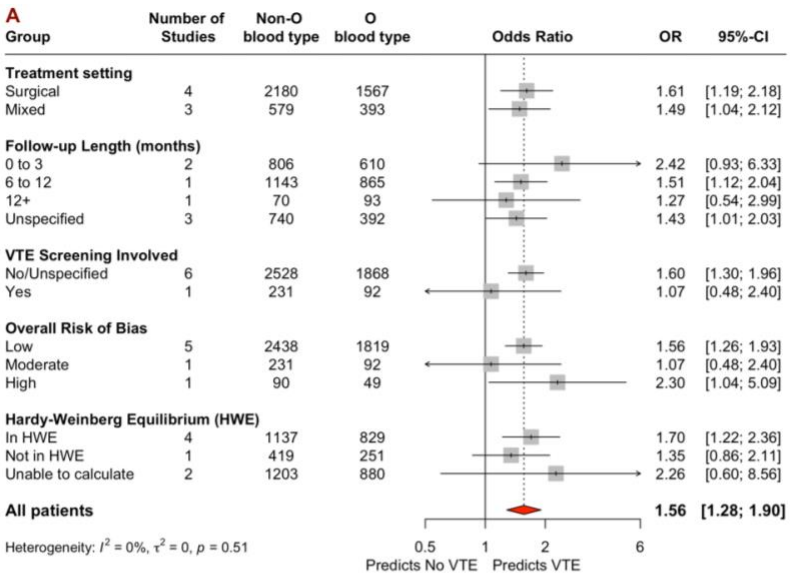
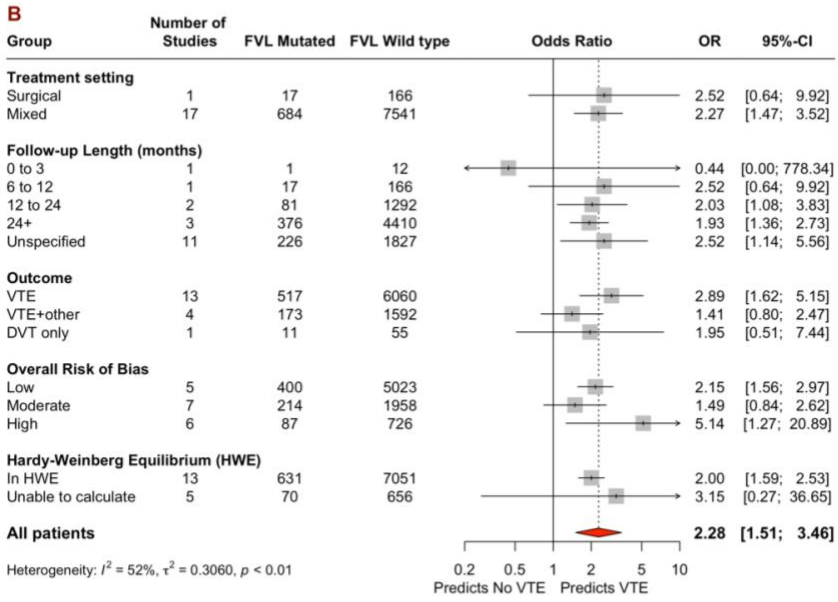


Figure 2. Overall risk of bias of studies included in the meta-analysis of each gene


A
Group
Number of Studies
Non-O blood type
O blood type
Odds Ratio
OR
95%-CI
Treatment setting
Surgical 4 2180 1567 1.61 [1.19; 2.18]
Mixed 3 579 393 1.49 [1.04; 2.12]
Follow-up Length (months)
0 to 3 2 806 610 2.42 [0.93; 6.33]
6 to 12 1 1143 865 1.51 [1.12; 2.04]
12+ 1 70 93 1.27 [0.54; 2.99]
Unspecified 3 740 392 1.43 [1.01; 2.03]
VTE Screening Involved
No/Unspecified 6 2528 1868 1.60 [1.30; 1.96]
Yes 1 231 92 1.07 [0.48; 2.40]
Overall Risk of Bias
Low 5 2438 1819 1.56 [1.26; 1.93]
Moderate 1 231 92 1.07 [0.48; 2.40]
High 1 90 49 2.30 [1.04; 5.09]
Hardy-Weinberg Equilibrium (HWE)
In HWE 4 1137 829 1.70 [1.22; 2.36]
Not in HWE 1 419 251 1.35 [0.86; 2.11]
Unable to calculate 2 1203 880 2.26 [0.60; 8.56]
All patients 1.56 [1.28; 1.90]
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.51
0.5 1 2 6
Predicts No VTE Predicts VTE


B
Group
Number of Studies
FVL Mutated
FVL Wild type
Odds Ratio
OR
95%-CI
Treatment setting
Surgical 1 17 166 2.52 [0.64; 9.92]
Mixed 17 684 7541 2.27 [1.47; 3.52]
Follow-up Length (months)
0 to 3 1 1 12 0.44 [0.00; 778.34]
6 to 12 1 17 166 2.52 [0.64; 9.92]
12 to 24 2 81 1292 2.03 [1.08; 3.83]
24+ 3 376 4410 1.93 [1.36; 2.73]
Unspecified 11 226 1827 2.52 [1.14; 5.56]
Outcome
VTE 13 517 6060 2.89 [1.62; 5.15]
VTE+other 4 173 1592 1.41 [0.80; 2.47]
DVT only 1 11 55 1.95 [0.51; 7.44]
Overall Risk of Bias
Low 5 400 5023 2.15 [1.56; 2.97]
Moderate 7 214 1958 1.49 [0.84; 2.62]
High 6 87 726 5.14 [1.27; 20.89]
Hardy-Weinberg Equilibrium (HWE)
In HWE 13 631 7051 2.00 [1.59; 2.53]
Unable to calculate 5 70 656 3.15 [0.27; 36.65]
All patients 2.28 [1.51; 3.46]
Heterogeneity: I^2 = 52%, τ^2 = 0.3060, p < 0.01
0.2 0.5 1 2 5 10
Predicts No VTE Predicts VTE

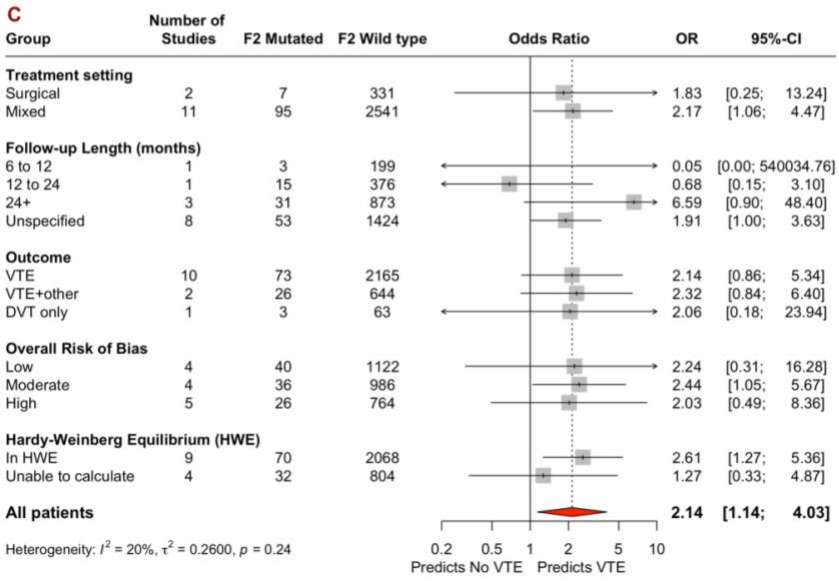

C
Group
Number of Studies
F2 Mutated
F2 Wild type
Odds Ratio
OR
95%-CI
Treatment setting
Surgical 2 7 331 1.83 [0.25; 13.24]
Mixed 11 95 2541 2.17 [1.06; 4.47]
Follow-up Length (months)
6 to 12 1 3 199 0.05 [0.00; 540034.76]
12 to 24 1 15 376 0.68 [0.15; 3.10]
24+ 3 31 873 6.59 [0.90; 48.40]
Unspecified 8 53 1424 1.91 [1.00; 3.63]
Outcome
VTE 10 73 2165 2.14 [0.86; 5.34]
VTE+other 2 26 644 2.32 [0.84; 6.40]
DVT only 1 3 63 2.06 [0.18; 23.94]
Overall Risk of Bias
Low 4 40 1122 2.24 [0.31; 16.28]
Moderate 4 36 986 2.44 [1.05; 5.67]
High 5 26 764 2.03 [0.49; 8.36]
Hardy-Weinberg Equilibrium (HWE)
In HWE 9 70 2068 2.61 [1.27; 5.36]
Unable to calculate 4 32 804 1.27 [0.33; 4.87]
All patients 2.14 [1.14; 4.03]
Heterogeneity: I^2 = 20%, τ^2 = 0.2600, p = 0.24
0.2 0.5 1 2 5 10
Predicts No VTE Predicts VTE

Figure 3. Forest plot of a) ABO blood type, b) factor V leiden (FVL) and c) Prothrombin Factor II (F2) G20210A and VTE risk by subgroup

3.7 Appendix

Supplemental Data 1. Search Strategy

MEDLINE

1. Venous Thromboembolism/
2. (venous adj1 thrombo*).ti,ab,kf.
3. (vein* adj1 thrombo*).ti,ab,kf.
4. Venous Thrombosis/
5. venothrombo*.ti,ab,kf.
6. pulmonary embolism/ or pulmonary infarction/
7. (pulmonary adj1 thrombo*).ti,ab,kf.
8. (pulmonary adj1 embol*).ti,ab,kf.
9. (lung adj1 embol*).ti,ab,kf.
10. (lung adj1 thrombo*).ti,ab,kf.
11. exp biomarkers/ or blood coagulation factor inhibitors/ or blood coagulation factors/
12. (biologic* adj1 marker*).ti,ab,kf.
13. (biochemical adj1 marker*).ti,ab,kf.
14. biomarker*.ti,ab,kf.
15. (clinical adj1 marker*).ti,ab,kf.
16. (surrogate adj1 endpoint*).ti,ab,kf.
17. (surrogate adj1 end adj1 point*).ti,ab,kf.
18. (surrogate adj1 marker*).ti,ab,kf.
19. (immun* adj1 marker*).ti,ab,kf.

20. (laboratory adj1 marker*).ti,ab,kf.
21. (serum adj1 marker*).ti,ab,kf.
22. (plasma adj1 marker*).ti,ab,kf.
23. Genetic Markers/
24. (genetic adj1 marker*).ti,ab,kf.
25. (dna adj1 marker*).ti,ab,kf.
26. (chromosome adj1 marker*).ti,ab,kf.
27. Genetic Predisposition to Disease/
28. (genetic adj1 predisposition*).ti,ab,kf.
29. (genetic adj1 susceptibilit*).ti,ab,kf.
30. (genetic adj2 (risk* or factor*)).ti,ab,kf.
31. (coagulation adj1 factor*).ti,ab,kf.
32. (clotting adj1 factor*).ti,ab,kf.
33. exp Genes/
34. exp Mutation/
35. (gene or genes or allele or alleles).ti,ab,kf.
36. exp Neoplasms/
37. cancer*.mp.
38. malignan*.mp.
39. (tumor or tumour).mp.
40. (neoplasm or neoplasms).mp.
41. (predict* or prognos* or risk*).ti,ab,kf.

42. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

43. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35

44. 36 or 37 or 38 or 39 or 40

45. 41 and 42 and 43 and 44

46. 45 not (exp animals/ not humans.sh.) [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

EMBASE

1. vein thrombosis/
2. (vein$ adj1 thrombo$).ti,ab,kw.
3. venous thromboembolism/
4. (venous adj1 thrombo$).ti,ab,kw.
5. venothrombo$.ti,ab,kw.
6. lung embolism/
7. (lung adj1 embol$).ti,ab,kw.
8. (pulmonary adj1 embol$).ti,ab,kw.
9. (lung adj1 thromboembol$).ti,ab,kw.
10. (pulmonary adj1 thromboembol$).ti,ab,kw.
11. deep vein thrombosis/
12. biological marker/

13. biomarker$.ti,ab,kw.
14. (biologic$ adj1 marker$).ti,ab,kw.
15. (biochemical adj1 marker$).ti,ab,kw.
16. (clinical adj1 marker$).ti,ab,kw.
17. (surrogate adj1 endpoint$).ti,ab,kw.
18. (surrogate adj1 end adj1 point$).ti,ab,kw.
19. (surrogate adj1 marker$).ti,ab,kw.
20. (immun$ adj1 marker$).ti,ab,kw.
21. (laboratory adj1 marker$).ti,ab,kw.
22. (serum adj1 marker$).ti,ab,kw.
23. (plasma adj1 marker$).ti,ab,kw.
24. genetic marker/
25. (genetic adj1 marker$).ti,ab,kw.
26. (dna adj1 marker$).ti,ab,kw.
27. (chromosome adj1 marker$).ti,ab,kw.
28. genetic predisposition/
29. (genetic adj1 predisposition$).ti,ab,kw.
30. (genetic adj1 susceptibilit$).ti,ab,kw.
31. (genetic adj2 (risk$ or factor$)).ti,ab,kw.
32. blood clotting factor/
33. (coagulat$ adj1 factor$).ti,ab,kw.
34. (clotting adj1 factor$).ti,ab,kw.

35. exp gene mutation/ or exp marker gene/ or exp gene/

36. (gene or genes or allele or alleles).ti,ab,kw.

37. exp malignant neoplasm/

38. cancer$.mp.

39. malignan*.mp.

40. (tumor or tumour).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

41. (neoplasm or neoplasms).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

42. (predict* or prognos* or risk*).ti,ab,kw.

43. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

44. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

45. 37 or 38 or 39 or 40 or 41

46. 42 and 43 and 44 and 45

COCHRANE CENTRAL

#1 MeSH descriptor: [Venous Thromboembolism] explode all trees

#2 (venous near/1 thrombo*):ti,ab,kw

#3 (vein* near/1 thrombo*):ti,ab,kw

#4 MeSH descriptor: [Venous Thrombosis] explode all trees

#5 venothrombo*:ti,ab,kw

#6 MeSH descriptor: [Pulmonary Embolism] explode all trees

#7 (pulmonary near/1 thrombo*):ti,ab,kw

#8 (pulmonary near/1 embol*):ti,ab,kw

#9 (lung near/1 embol*):ti,ab,kw

#10 (lung near/1 thrombo*):ti,ab,kw

#11 MeSH descriptor: [Biomarkers] explode all trees

#12 (biologic near/1 marker*):ti,ab,kw

#13 (biochemical near/1 marker*):ti,ab,kw

#14 biomarker*:ti,ab,kw

#15 (clinical near/1 marker*):ti,ab,kw

#16 (surrogate near/1 endpoint*):ti,ab,kw

#17 (surrogate near/1 end near/1 point*):ti,ab,kw

#18 (surrogate near/1 marker*):ti,ab,kw

#19 (immun* near/1 marker*):ti,ab,kw

#20 (laboratory near/1 marker*):ti,ab,kw

#21 (serum near/1 marker*):ti,ab,kw

#22 (plasma near/1 marker*):ti,ab,kw

#23 MeSH descriptor: [Genetic Markers] explode all trees

#24 (genetic near/1 marker*):ti,ab,kw

#25 (dna near/1 marker*):ti,ab,kw

#26 (chromosome near/1 marker*):ti,ab,kw

#27 MeSH descriptor: [Genetic Predisposition to Disease] explode all trees

#28 (genetic near/1 predisposition):ti,ab,kw

#29 (genetic near/1 susceptibilit*):ti,ab,kw

#30 (genetic near/2 (risk* or factor*)):ti,ab,kw

#31 (coagulation near/1 factor*):ti,ab,kw

#32 (clotting near/1 factor*):ti,ab,kw

#33 MeSH descriptor: [Genes] explode all trees

#34 MeSH descriptor: [Mutation] explode all trees

#35 (gene or genes or allele or alleles):ti,ab,kw

#36 MeSH descriptor: [Neoplasms] explode all trees

#37 cancer*

#38 malignan*

#39 (tumor or tumour)

#40 (neoplasm or neoplasms)

#41 (predict* or prognos* or risk*):ti,ab,kw

#42 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)

#43 (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35)

#44 (#36 or #37 or #38 or #39 or #40)

#45 (#41 and #42 and #43 and #44)

#46 (#45 not (animal or plants or nonhuman or animal tissue or animal experiment or animal model or fungus))

Supplemental Table 1. Number of studies reporting on different thrombophilia genes or mutations

Gene or Mutation	**N of Studies**	**Studies[1]**
ABO blood type	10	Muñoz-Martin 2018, **Li 2015**, **Crowley 2014**, **Kodama 2010, Heenkenda 2019,** Streiff 2004, **Wang 2014, Bhanvadia 2019**, Tollefson 2013, **Wang 2019**
Factor V Leiden	18	**Heenkenda 2019, Héraudeau 2018, Brand 2016, Kovac 2015, Wahba 2015, Pabinger 2015, de Haas 2010, Mandala 2010, Eroglu 2009, Blom 2005, Kennedy 2005, Corso 2004, Ravin 2002, Haim 2001, Ulrych 2019, Arslan 2011, Ozkan 2012, Muñoz-Martin 2018**
Factor V K858R	1	Muñoz-Martin 2018
Factor VII R353Q	1	Eroglu 2010
Factor VII-401 G/T	1	Eroglu 2010
Factor VII-402 G/A	1	Eroglu 2010
Factor XII-4 C/T	1	Muñoz-Martin 2018
Factor XIII A1-103 G/T	2	Muñoz-Martin 2018, Tiedje 2011
Fibrinogen-455 G/A	1	Tiedje 2011
Fibrinogen gamma gene-10034 C/T	1	Paulsen 2020
Glycoprotein IIIa	1	Arslan 2010
Integrin Beta-3 (rs3809865)	1	Bianconi 2015
Integrin Beta-3 (rs5918)	1	Bianconi 2015
Integrin Beta-3 (rs4642)	1	Bianconi 2015
Interleukin-6-174 G/T	1	Malaponte 2013
Methylelene-tetrahydrofolate reductase C677T	5	**Wang 2021, Wahba 2015, Eroglu 2009, Ozkan 2012, Arslan 2011**
Methylelene-tetrahydrofolate reductase A1298C	1	Arslan 2010

Plasminogen Activator Inhibitor-1	4	**Wang 2021, de Haas 2010, Arslan 2011, Ozkan 2012**
Protein Z intron G79A	1	Eroglu 2008
Prothrombin G20210A	13	**Muñoz-Martin 2018, Heenkenda 2019, Heraudeau 2018, Kovac 2015, Wahba 2015, de Haas 2010, Mandala 2010, Eroglu 2009, Blom 2005, Kennedy 2005, Ulrych 2019, Arslan 2011, Ozkan 2012**
Serpin Family A member 10	1	Muñoz-Martin 2018
Serpin Family C member 1	1	Muñoz-Martin 2018
Tumor Necrosis Factor Alpha (rs1799724)	1	Roselli 2013
Tumor Necrosis Factor Alpha (rs1800629)	1	Roselli 2013
Tumor Necrosis Factor Alpha (rs1800630)	1	Roselli 2013
Tumor Necrosis Factor Alpha (rs1800750)	1	Roselli 2013
Tumor Necrosis Factor Alpha (rs361525)	1	Roselli 2013
Vascular Endothelial Growth Factor-2578 C/A	2	**Ferroni 2016, Almasi 2011**
Vascular Endothelial Growth Factor A-634 G/C	2	**Ferroni 2016, Labussière 2014**

[1] The studies included in the meta-analysis are in bold.

Supplemental Table 2. Study characteristics of included studies

ID – First author	Year	Country	Design	N	Cancer Type	Any use of Anticoagulation or Antiplatelet		Genes and Mutations
						ACT	APT	
25 - Wang	2021	China	PC	214	Lung	-	-	Methylenetetrahydrofolate reductase, Plasminogen activator inhibitor-1
192 -Heenkenda	2019	Sweden	PC	139	Brain	-	-	ABO, Factor V Leiden, Prothrombin FII G20210A
263 - Heraudeau	2018	France	CC	364	Many	-	-	Factor V Leiden, Prothrombin FII G20210A
274 - Muñoz-Martin	2018	Spain	PC	391	Lung + GI	No	-	A1 blood group, Factor XII (rs1801020) Factor XIII (rs5985), Prothrombin FII G20210A (rs1799963), Factor V (rs4524), Factor V Leiden (rs6025), SERPINA10 (rs2232698), SERPINC1 (rs121909548)
368 - Wang	2019	China	PC	323	Lung	-	-	ABO blood group
409 - Brand	2016	Sweden	RC	4261	Breast	-	-	Factor V Leiden
467 - Ferroni	2016	Italy	PC	297	Many	-	-	Vascular endothelial growth factor - A (11 polymorphisms)
470 - Bianconi	2015	Austria	PC	112	Colorectal	Yes	-	Integrin Beta-3 (rs3809865, rs4642, rs5918)
522 - Kovac	2015	Serbia	CC	150	Breast	-	-	Factor V Leiden, Prothrombin FII G20210A
524 - Wahba	2015	Egypt	CC	80	Many	-	-	Factor V Leiden, Methylenetetrahydrofolate reductase C677T, Prothrombin FII G20210A

528 - Pabinger	2015	Austria	PC	982	Many	Yes	Yes	Factor V Leiden
624 - Roselli	2013	Italy	RC	157	GI	-	-	Tumor necrosis factor (6 polymorphisms)
640 - Malaponte	2013	Italy	CC	320	Many	-	-	Interleukin-6
785 - Tiedje	2011	Vienna	PC	1079	Many	-	-	Fibrinogen genotype, Factor VIII - A Val34Leu genotype
786 - Almasi	2011	Czech Republic	RC	111	Myeloma	Yes	-	Vascular endothelial growth factor A
831 - de Haas	2010	Netherlands	PC	324	Testicular	-	-	Factor V Leiden, Plasminogen activator inhibitor-1, Prothrombin FII G20210A
849 - Eroglu	2010	Turkey	CC	190	Many	-	-	-323 insertion 10-bp Factor VII polymorphism, -401G/T Factor VII polymorphism, -402 G/A Factor VII polymorphism
862 - Mandalà	2010	Italy	PC	381	Breast + GI	-	-	Factor V Leiden, Prothrombin FII G20210A
913 - Eroglu	2009	Turkey	CC	187	Many	-	-	Factor V Leiden, Methylenetetrahydrofolate reductase C677T, Prothrombin FII G20210A
917 - Eroglu	2008	Turkey	CC	170	Many	-	-	Protein Z intron G79A
1035 - Blom	2005	Netherlands	CC	205	Many	-	-	Factor V Leiden, Prothrombin FII G20210A
1037 - Kennedy	2005	USA	CC	202	Many	-	-	Factor V Leiden, Prothrombin FII G20210A
1052 - Corso	2004	Italy	PC	13	Myeloma	-	-	Factor V Leiden
1092 - Ravin	2002	USA	CC	74	Gyne	-	-	Factor V Leiden
1129 - Haim	2001	Israel	CC	113	Many	Yes	-	Factor V Leiden

1397 - Di Stefano	2015	France	RC	225	glioblastoma	-	-	Vascular Endothelial Growth Factor - A (rs2010963)
1909 - Ulrych	2019	Czech Republic	PC	202	Colorectal	Yes	-	Factor V Leiden, Prothrombin FII G20210A
S004 - Arslan	2011	Turkey	CC	66	Lung	-	-	Factor V Leiden, Glycoprotein IIIa, Methylenetetrahydrofolate reductase C677T, Methylenetetrahydrofolate reductase A1298C, Plasminogen activator-inhibitor-1, Prothrombin FII G20210A
S010 - Crowley	2014	Ireland	RC	217	Myeloma	-	-	ABO
S020 - Kodama	2010	Japan	PC	75	Gyne	Yes	-	ABO
S023 – Li	2015	USA	RC	670	Pancreas	Yes	Yes	ABO (rs505922 and rs8176746)
S029 - Ozkan	2012	Turkey	CC	292	Many	-	-	Factor V Leiden, Methylenetetrahydrofolate reductase C677T, Plasminogen activator-inhibitor-1, Prothrombin FII G20210A
S035 - Streiff	2004	USA	RC	130	Brain	Yes	-	ABO
A1 – Wang	2014	USA	RC	2076	Bladder	Yes	-	ABO
A2 – Tollefson	2013	USA	RC	18472	Prostate	Yes	-	ABO
A3 - Bhanvadia	2019	USA	RC	1341	Bladder	Yes	-	ABO

Abbreviations: ACT=anticoagulant therapy, APT= antiplatelet therapy, CC=case-control, C-cohort=case-cohort, GI=gastro-intestinal, PC=prospective cohort, RC=retrospective cohort, RCT=randomized control trial

Supplemental Table 3. Definition of outcomes of included studies

ID – First author	Out c-ome	F/U Time[a] (months)	Definition of Outcome	Surgical Procedures and Treatments during observation period
25 - Wang	VTE	Unclear	The diagnosis of VTE confirmed by venography, DUS or CTPA in addition to clinical signs and symptoms.	Unspecified
192 - Heenkenda	VTE	Unclear	All cases had symptomatic VTE and were diagnosed with US for DVT or CTPA for PE.	surgery: radical (45%), partial (39%) or biopsy (16%) with concomitant radiotherapy and temozolomide (100%)
263 - Heraudeau	VTE	Unclear	DVT of the lower limbs confirmed by CUS. The diagnostic criteria for symptomatic PE were either: (1) high clinical probability and high-probability V/Q scan according to the PIOPED criteria, or (2) a proximal DVT shown by U/S with PE symptoms, or (3) a positive CTPA with a central filling defect	surgery (44.2%), chemotherapy (50.6%), radiotherapy (25.0%)
274 - Muñoz-Martin	VTE	18	DVT in the lower limbs diagnosed by US or ascending venography. PE diagnosed by V/Q scan, CTPA, or spiral CT. Intracranial VTE was diagnosed by MRI.	Unspecified
368 - Wang	VTE	Unclear	DUS was performed on all patients pre- and post-surgery to assess for DVT. If patient had PE symptoms (chest pain, hemoptysis or unexplained hypoxemia and dyspnea) or Caprini ≥ 9 or new DVT post-surgery, then CTPA was performed to check for PE.	Open thoracotomy or video-assisted thoracoscopic surgery

409 - Brand	VTE	91.2	VTE defined according to the International Classification of Diseases (ICD): VTE of the legs (451,671C, 671D, 671E, 671X, I80, O222, O223, O229, O870, O871, O879, O087) and PE (415B, 416W, 673C, 639G, I26, O882, O082)	Surgery (unspecified), Radiotherapy (unspecified), Chemotherapy (38.7%), Endocrine therapy (83.8%)
467 - Ferroni	VTE	3.4	Proximal DVT confirmed by venography or CDUS. PE confirmed by spiral CT.	Chemotherapy
470 - Bianconi	VTE	46	Patients not routinely screened for VTE. VTE diagnosed by objective medical imaging methods, such as duplex U/S or CT in patients with symptomatic or fatal cases.	Anti-VEGFA treatment (45.5%)
522 - Kovac	VTE	Unclear	Documented VTE developed during the treatment. VTE diagnosed by DUS, V/Q scan and helical tomography/CT.	Chemotherapy (100%), Bevacizumab (23%)
524 - Wahba	VTE	Unclear	VTE diagnosed by the treating clinician on the basis of clinical suspicion using the usual diagnostic procedures.	surgery (77.5%), chemotherapy (52.3%), radiotherapy (20.0%)
528 - Pabinger	VTE	22.5	Objectively confirmed symptomatic or fatal VTE.	Chemotherapy (67%), Surgery (38.5%), Radiotherapy (46%)
624 - Roselli	VTE	12	All patients were seen regularly at their scheduled chemotherapy visits or at the occurrence of clinically suspected VTE. Symptomatic DVT or PE, by which DVT was confirmed by venography or colour-coded duplex sonography (in proximal DVT only). PE was diagnosed by spiral CT.	Chemotherapy (100%), Bevacizumab (38%)
640 - Malaponte	DVT	Unclear	DVT was based on the no compressibility of a deep vein of lower limbs by doppler probe and/or the presence of venous occlusion by echogenic structure.	Excluded: bevacizubam, thalidomide, lenalidomide

				and/or radiation therapy were excluded.
785 - Tiedje	VTE	19.9	Patients not screened for VTE. In patients with VTE symptoms, duplex U/S or venography was performed for confirmation or exclusion of diagnosis of DVT and CT or V/Q scan for diagnosis of PE.	chemotherapy (63.7%), radiotherapy (45.2%), surgery (37.3%)
786 - Almasi	VTE	Unclear	Unspecified	Thalidomide-based treatment (100%), cyclophophamide+ Thalimomide+dexamethasone (85.6%)
831 - de Haas	VTE	120	VTE (DVT and/or PE) occurring during chemotherapy.	chemotherapy (100%), surgery (51.3%)
849 - Eroglu	VTE	Unclear	In patients with symptoms of DVT, a CDUS was performed to confirm the diagnosis. PE suspected by clinical presentation was confirmed by V/Q scan.	Unspecified
862 - Mandalà	VTE	35	Patients were not screened; only symptomatic forms were checked. The medical charts and radiological history of all patients were checked for U/S and V/Q lung scan. VTE was diagnosed by the clinician based on clinical suspicion using the usual diagnostic procedures (non-compressibility of a proximal vein). When symptoms indicative of PE developed, a V/Q scan was carried out. In cases not conclusive for PE diagnosis, a spiral CT scan was required to confirm.	chemotherapy (100%), hormone replacement therapy (3.4%)

913 - Eroglu	VTE	Unclear	VTE diagnosed appropriately by CDUS, V/Q scan or CT in addition to clinical signs and symptoms.	surgery, chemotherapy, hormonotherapy
917 - Eroglu	VTE	Unclear	Cases with VTE were diagnosed appropriately by CDUS, V/Q scan or CT in addition to clinical signs and symptoms.	cancer therapy (unspecified)
1035 - Blom	VTE	60	Diagnosis of clinically suspected DVT of the leg based on a clinical score, serial CUS, and D-dimer assay. Objective testing of clinically suspected PE based on V/Q scan, U/S of the leg veins, or CTPA.	During first year: chemotherapy (16.9%), radiotherapy (4.1%), surgery (23.8%), combination (36.6%)
1037 - Kennedy	VTE	Unclear	Objective diagnosis of thrombosis, excluding asymptomatic catheter-related thrombosis. A DVT diagnosis required positive duplex or DUS or venogram, and for PE, positive chest CT scan, CTPA or high probability V/Q scan.	Within 3-months of VTE: chemotherapy (57.4%), surgery (10.9%), hormonal cancer therapy (12.4%)
1052 - Corso	DVT	3	Unspecified	low-dose thalidomide and dexamethasone (100%)
1092 - Ravin	VTE	Unclear	DVT defined as clinically significant DVT confirmed by continuous-wave Doppler and real-time U/S. PE suspected by clinical presentation confirmed by V/Q scan or thoracic helical CT performed with contrast medium injection.	surgery (79.7%), chemotherapy (64.9%), radiation therapy (33.8%)
1129 - Haim	VTE	Unclear	DVT based on DUS	chemotherapy (68.1%)
1397 - Di Stefano	VTE	Unclear	Unspecified	chemotherapy (temozolomide) (100%)
1909 - Ulrych	VTE	12	Wells' criteria were used for clinical diagnosis of DVT. Patients with a Wells score of >2 points warranted U/S examination of legs to verify	surgery (100%)

			DVT. When clinical suspicion of PE was observed, a CTA was performed.	
S004 - Arslan	DVT	Unclear	Diagnosis of DVT was achieved with the help of lower extremity DUS. Absence of lower extremity thrombi in DUS was considered as absence of DVT.	Unspecified
S010 - Crowley	VTE	44.6	The participating hospital picture archiving and communication system was utilized. A VTE was diagnosed if there was evidence of a PE on CTPA or CT thorax or evidence of a DVT on CDUS or contrast venography.	immunomodulatory drugs alone(1.4%), immunomodulatory drugs+steroids/cytotoxic agents (67.3%), radiotherapy (43.3%), autologous stem cell transplant (24.0%)
S020 - Kodama	VTE	1	After surgery, clinical signs (leg swelling, tenderness along distribution of deep veins, acute cardiovascular dysfunction, dypsnea, chest pain, and loss of consciousness) and elevation of plasma d-dimer levels (10-15ug/mL, especially > 15ug/mL) were monitored. Patients with clinical signs or d-dimer elevation were subject to CT.	Gynecologic cancer surgery (hysterectomy and/or para-lymphadenectomy) (100%)
S023 – Li	VTE	Unclear	TE events (including DVT, PE and others such as portal and splenic vein thrombosis) were identified based on radiological evidence.	chemotherapy (37.3%), chemoradiation (50.8%)
S029 - Ozkan	VTE	Unclear	A VTE diagnosis required a positive DUS or venogram and a positive chest CT, a CTPA or high probability V/Q scan for PE.	radiotherapy (29.8%), surgery (55.8%), hormone therapy (5.1%)
S035 - Streiff	VTE	12	The diagnosis of DVT required objective radiologic documentation using duplex U/S or venography. The diagnosis of PE required	surgery (100%), radiotherapy (100%), chemotherapy (60.8%)

			documentation of a high-probability V/Q scan, a positive spiral CT scan, or CTPA.	
A1 – Wang	VTE	11.1	The primary endpoint was VTE after surgery. During the early half of the study period, the diagnosis of DVT was made by venography with duplex U/S used to diagnose DVT later. The diagnosis of PE was based on arteriography or VQ scan. The diagnostic evaluation of VTE was based on symptom presentation and/or clinical evaluation - patients did not undergo screening.	Surgery (100%), chemotherapy (14.2%)
A2 – Tollefson	VTE	1	VTE diagnosis based on symptomatic presentation.	Surgery (100%), radiotherapy (15.3%), hormonal therapy
A3 - Bhanvadia	VTE	3	VTE was defined as any DVT or PE that presented symptomatically and was confirmed by appropriate imaging (ultrasound, VQ scan or CTPA). No screening was done for asymptomatic VTE.	Surgery (100%), chemotherapy (33.4%)

Abbreviations: CDUS=color doppler ultrasound, CT=computed tomography, CTA= computerized tomographic angiography, CTPA = computed tomography pulmonary angiogram, C/U=compression ultrasonography, DVT=deep vein thrombosis, DUS= doppler ultrasound, IPG=impedance plethysmography, MRI= magnetic resonance imaging, PE=pulmonary embolism, U/S=ultrasound, VQ=ventilation/perfusion VTE=venous thromboembolism

[a]Follow-up time based on median follow-up or when no median was specified, intended study follow up period was used

Supplemental Table 4. Measures of association between VTE and genes/mutations in individual studies

Biomarker	ID[&]	Specific SNP	Cutpoint	Method of Measurement	Time of Inception	Effect measure (95% CI)	Adjusted effect measure (95% CI)
ABO	192		Non-O vs O		post-surgery, pre-radiotherapy+temozolomide	OR: 2.30 (1.04-5.09)	--
	274	number of A1 allele	1 vs 0 2 vs 0	Taqman assay	at diagnosis	OR: 1.08 (0.62-1.89) OR: 1.35 (0.51-3.56)	--
	368		Non-O vs O		preoperative	OR: 1.07 (0.48-2.40)	--
	S010		Non-O vs O		at diagnosis	OR: 1.27 (0.54-2.99)	--
	S020		Non-O vs O		preoperative	OR: 7.00 (0.86-57.1)	OR: 10.6 (1.11-101.58)[a]
	S023	rs505922 & rs8176746	Non-O vs O	Taqman assay	at initial clinical evaluation of cancer	OR: 1.35 (0.86-2.11)	OR: 1.74 (1.07-2.84)[b]
	S035		AB vs O A vs O B vs O		at diagnosis	HR: 9.4 (2.7-32) HR: 2.7 (1.00-7.00) HR: non-measurable	--
	A1		Non-O vs O		preoperative	OR: 1.51 (1.12-2.04)	OR: 1.49 (1.05-2.13)[c]
	A2		Non-O vs		preoperative	--	OR: 1.98 (1.24-

			O				3.16)[d]
	A3		A vs B vs AB vs O		preoperative	OR: 1.94 (1.22-3.09)	OR: 1.94 (1.22-3.10)[e]
Factor V Leiden	192		hetero vs normal	Pyromark Q24 instrument (Qiagen, Hilden, Germany)	postsurgery, pre-radiotherapy and temozolomide	OR: 120.79 (7.06-2067.40)*	--
	263		mutated vs normal	--	varying	OR: 6.67 (1.98-22.43)	OR: 7.04 (2.01-24.63)[f]
	274	rs6025	hetero vs normal	Taqman assay	at diagnosis	OR: 2.31 (0.56-9.46)	--
	409		mutated vs normal	--	at diagnosis	OR: 1.94 (1.35-2.79)	HR: 1.88 (1.33-2.64)[g]
	522		mutated vs normal	--	tamixofen use	OR: 3.32 (1.18-9.35)	--
	524		mutated vs normal	FV-PTH-MTHFR StripAssay	varying	OR: 3.86 (1.12-13.29)	--
	528		mutated vs normal	--	pretreatment	OR: 1.97 (0.97-4.01)	HR: 2.00 (1.00-4.00)[h]
	831		hetero vs normal	TaqMan Genotyping Assay	at start of chemotherapy	OR: 1.45 (0.31-6.67)	--
	862		hetero vs normal	FV-PTH Stripassay	prechemotherapy	OR: 0.43 (0.03-7.38)*	--
	913		mutated vs normal	LightCycler kits	varying	OR: 30.93 (6.95-137.75)	--
	103		mutated vs	--	varying	OR: 2.57 (0.33-	--

	5		normal			20.19)	
	103		hetero vs	TaqMan	varying	OR: 1.7 (0.3-10.7)	--
	7		normal	assay			
	105		hetero vs		pretreatment	OR: 5.50 (0.10-	--
	2		normal			289.76)	
			homo vs				
			normal				
	109		mutated vs	--	varying	OR: 0.31 (0.06-	--
	2		normal			1.69)	
	112		mutated vs	--	varying	OR: 0.25 (0.03-	--
	9		normal			2.31)	
	190		mutated vs	--	preoperative	OR: 2.52 (0.64-	--
	9		normal			9.92)	
	S00		mutated vs	CVD	varying	OR: 1.95 (0.51-	--
	4		normal	StripAssay		7.44)	
				kit			
	S02		mutated vs	--	varying	OR: 1.38 (0.82-	--
	9		normal			2.31)	
Factor V	274	rs4524	1 vs 0	TaqMan	at diagnosis	OR: 4.21 (0.97-	--
			2 vs 0	genotyping		11.33)	
				assays		OR: 5.77 (0.76-	
						43.9)	
Factor VII	849	-323	ins/w vs	--	varying	OR : 1.35 (0.71-	--
		insertion	w/w			2.54)	
		10-bp	ins/ins vs			OR : 0.97 (0.18-	
			w/w			5.25)	
	849	-401G/T	GT vs GG	--	varying	OR: 1.35 (0.71-	--
			TT vs GG			2.54)	
						OR: 0.97 (0.18-	
						5.25)	

	849	-402G/A	AG vs GG AA vs GG	--	varying	OR: 0.60 (0.28-1.29) OR: 0.27 (0.03-2.22)	--
Factor XII	274	rs1801020	1 vs 0 2 vs 0	TaqMan assay	at diagnosis	OR: 0.99 (0.57-1.72) OR: 0.68 (0.15-3.13)	--
Factor XIII	274	rs5985	1 vs 0 2 vs 0	TaqMan assay	at diagnosis	OR: 1.29 (0.75-2.20) OR: 1.50 (0.52-4.34)	--
	785	A Val34Leu	Val34Leu vs Val34Val Leu34Leu vs Val34Val	--	pretreatment	HR: 0.99 (0.65-1.54)	HR: 1.00 (0.65-1.54)[i]
Fibrinogen genotype	785	--	455GA vs 455GG 455AA vs 455GG	--	pretreatment	HR: 0.77 (0.49-1.2)	HR: 0.77 (0.49-1.2)[i]
Glycoprotein IIIa	S004		hetero vs normal	CVD StripAssay kit	varying	OR: 2.07 (0.18-23.94)	--
Integrin Beta 3 gene	470	rs3809865	AT vs TT AA vs TT	--	pretreatment	HR: 7.87 (2.31-40.0) or OR: 9.22 (1.94-43.9)	HR: 7.52 (2.2-38.46)[j]
	470	rs4642	CT vs CC	--	pretreatment	OR: 3.81 (0.47-	--

			TT vs CC			31.14)	
	470	rs5918	AG vs GG	--	pretreatment	OR: 1.05 (0.30-	--
			AA vs GG			3.75)	
Interleukin-6	640	--	GG vs (GC+CC)	--	varying	OR: 2.14 (1.37-3.34)	--
Methyelene-tetrahydro-folate reductase	25	--	CT vs CC	--	varying	OR: 0.85 (0.46-1.59)	--
			TT vs CC			OR: 1.46 (0.69-3.12)	
	524	C677T	hetero vs normal	FV-PTH-MTHFR	varying	OR: 2.18 (0.83-5.71)	--
			homo vs normal	StripAssay,		OR: 5.45 (0.23-126.97)*	
	913	C677T	CT vs CC	LightCycler	varying	OR: 1.22 (0.65-2.29)	--
			TT vs CC	kits		OR: 0.76 (0.23-2.60)	
	S004	C677T	hetero vs normal	CVD StripAssay	varying	OR: 2.39 (0.80-7.12)	--
			homo vs normal	kit		OR: 2.31 (0.54-9.79)	
	S004	A1298C	hetero vs normal	CVD StripAssay	varying	OR: 2.25 (0.76-6.65)	--
			homo vs normal	kit		OR: 14.0 (1.46-134.3)	
	S029	C677T	hetero vs normal	--	varying	OR: 2.06 (1.17-3.63)	OR: 2.06 (1.17-3.63)[k]
			homo vs normal			OR: 1.29 (0.57-2.90)	OR: 1.29 (0.57-2.90)[k]
Plasminoge	25		4G5G vs	--	varying	OR: 1.24 (0.59-	--

n activator inhibitor-1		5G5G 4G4G vs 5G5G			2.59) OR: 2.62 (1.19-5.75)	
	831	4G5G vs 5G5G 4G4G vs 5G5G	TC-MGB-NFQ probe	at start of chemotherapy	OR: 1.03 (0.40-2.65) OR: 0.78 (0.24-2.55)	--
	S004	hetero vs normal homo vs normal	CVD StripAssay kit	varying	OR: 6.33 (0.30-125.42)* OR: 7.00 (0.32-154.09)*	--
	S029	hetero vs normal homo vs normal	--	varying	OR: 0.71 (0.44-1.16) OR: 0.73 (0.30-1.77)	--
Protein Z intron G79A	917	GA vs GG AA vs GG	--	start of therapy?	OR: 0.74 (0.38-1.46) OR: 0.45 (0.09-2.23)	--
Prothrombin FII G20210A	192	hetero vs normal	Pyromark Q24 instrument	post-surgery, pre-radio-therapy+temozolomide	OR: 1.93 (0.26-14.18)	--
	263	mutated vs normal	--	varying	OR: 5.11 (0.59-44.21)	--
	274	rs1799963	mutated vs normal	Taqman assay	at diagnosis	OR: 0.69 (0.15-3.10)
	522		mutated vs normal	--	tamixofen use	OR: 2.81 (0.60-13.08)
	524		mutated vs	FV-PTH-	varying	OR: 0.73 (0.15-	--

			normal	MTHFR StripAssay		3.49)	
	831		hetero vs normal	TaqMan Assay	at start of chemotherapy	OR: 17.7 (3.73-84.1)	--
	862		hetero vs normal	FV-PTH Stripassay	prechemotherapy	OR: 1.46 (0.18-11.98)	--
	913		mutated vs normal	LightCycler kits	varying	OR: 0.48 (0.05-4.42)	--
	1035		mutated vs normal	--	varying	OR: 4.61 (0.27-79.70)*	--
	1037		hetero vs normal	TaqMan assay	varying	OR: 6.7 (0.9-infinity)	--
	1909		mutated vs normal	--	preoperative	OR: 1.91 (0.09-39.74)*	--
	S004		hetero vs normal	CVD StripAssay kit	varying	OR: 2.07 (0.18-23.94)	--
	S029		mutated vs normal	--	varying	OR: 2.67 (0.84-8.49)	--
SERPINA10	274	rs2232698	hetero vs normal	TaqMan assay	at diagnosis	OR: 2.31 (0.56-9.46)	--
SERPINC1	274	rs121909548	hetero vs normal	TaqMan assay	at diagnosis	OR: 2.25 (0.07-67.62)*	--
Tumor Necrosis Factor	624	rs1799724	hetero vs normal	DNA isolation kit	prechemotherapy	OR: 0.74 (0.20-2.76)	--
			homo vs normal			OR: 1.07 (0.05-21.55)*	
	624	rs1800629	hetero vs normal	DNA isolation kit	prechemotherapy	OR: 0.16 (0.01-2.84)*	--
			homo vs			OR: not estimable	

			normal				
	624	rs1800630	hetero vs normal homo vs normal	DNA isolation kit	prechemotherapy	OR: 0.74 (0.2-2.76) OR: 1.07 (0.05-21.55)*	--
	624	rs1800750	hetero vs normal homo vs normal	DNA isolation kit	prechemotherapy	OR: 0.94 (0.11-7.92) OR: not estimable	--
	624	rs361525	hetero vs normal homo vs normal	DNA isolation kit	prechemotherapy	OR: 0.87 (0.18-4.15) OR: 2.29 (0.10-53.48)*	--
	624	CTGGG haplotype	CTGGG vs all other haplotypes	DNA isolation kit	prechemotherapy	OR: 5.93 (1.79-19.64)	--
Vascular endothelial growth factor - A	467	-1154G/A	GA vs GG AA vs GG	HotStarTaq Master Mix kit	at start of chemotherapy	OR: 0.33 (0.12-0.90) OR: 0.12 (0.01-2.04)*	--
	467	-634G/C	GC vs GG CC vs GG	HotStarTaq Master Mix kit	at start of chemotherapy	OR: 2.30 (0.89-5.98) OR: 0.37 (0.04-3.19)	--
	467	rs1005230		HotStarTaq Master Mix kit	at start of chemotherapy	OR: 0.61 (0.32-1.15)	--
	467	rs13207351		HotStarTaq Master Mix kit	at start of chemotherapy	OR: 0.17 (0.02-1.27)	--

467	rs1470360		HotStarTaq Master Mix kit	at start of chemotherapy	OR: 0.26 (0.09-0.70)	--
467	rs2010963		HotStarTaq Master Mix kit	at start of chemotherapy	OR: 2.86 (1.16-7.02)	--
467	rs35569394		HotStarTaq Master Mix kit	at start of chemotherapy	OR: 0.61 (0.32-1.15)	--
467	rs35864111		HotStarTaq Master Mix kit	at start of chemotherapy	OR: 0.61 (0.32-1.15)	--
467	rs699947		HotStarTaq Master Mix kit	at start of chemotherapy	OR: 0.61 (0.32-1.15)	--
467	rs833061		HotStarTaq Master Mix kit	at start of chemotherapy	OR: 0.72 (0.39-1.30)	--
467	-1190G/A	GA vs GG AA vs GG	HotStarTaq Master Mix kit	at start of chemotherapy	OR: 1.63 (0.67-3.93) OR: 0.23 (0.03-1.88)	--
786	--	AC vs AA CC vs AA	TaqMan Assay	at diagnosis	OR: 0.44 (0.15-1.31) OR: 0.45 (0.13-1.64)	OR: 0.46 (0.16-1.38)[g,j] OR: 0.48 (0.13-1.77)[g,j]
1397	rs2010963	CG vs GG CC vs GG	Taqman Assay	varying	OR: 0.54 (0.12-2.42) OR : 3.00 (0.58-15.55)	--

Abbreviations: CI=Confidence Interval, HR=Hazard Ratio, OR=Odds Ratio, RR=Relative Risk,

SHR=Subdistribution Hazard Ratio, SNP=Single Nucleotide Polymorphism

[&] When stratified results are presented in the study, the first letter of the cancer group was given with the study ID to differentiate the groups (P=polycythemia vera, C=chronic myelogenous leukemia)

* Estimated using 0.5 instead of zero cell

[a] Adjusted for d-dimer and usage of erythropoietin

[b] Adjusted for hemoglobin, bmi, cancer stage and tumor site

[c] Adjusted for age, year of surgery, ECOG, BMI, tumor stage, nodal stage, number of nodes removed, blood types, operating room time

[d] Adjusted for age, stage, positive lymphnodes, no nodes removed, surgical blood loss

[e] Adjusted for age, bmi, pathological stage, neodjuvant chemotherapy

[f] Adjusted for cancer stage and family history of VTE

[g] Adjusted for age

[h] Adjusted for age, sex, cancer types, new vs recurrent cancer, treatment modalities

[i] Adjusted for chemotherapy, radiotherapy, surgery, age and sexe

[j] Adjusted for sexe

Adjusted for chemotherapy, radiotherapy, surgery, age and sexe

[k] Adjusted for metastasis

Supplemental Table 5. Sensitivity analysis using other methods

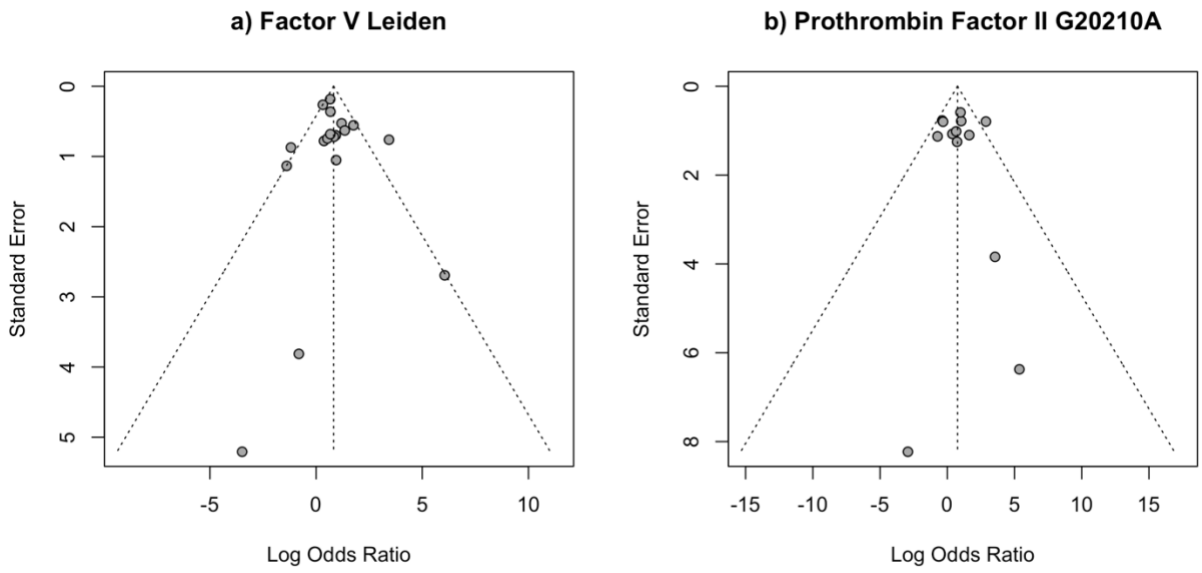
Thrombophilia Gene/Mutation	**Method**	**I^2 (%)**	**Pooled OR (95% CI)**	***P-value***
ABO blood type	MH with 0.5 correction	0	1.56 (1.28-1.90)	<0.0001
	Inverse Variance with TACC	0	1.56 (1.28-1.90)	<0.0001
Factor V Leiden	MH with 0.5 correction	57.4	2.39 (1.47-3.88)	0.0005
	Inverse Variance with TACC	47	2.26 (1.45-3.54)	0.0003
	Without matched case-control studies (n=14)	50	2.28 (1.43-3.62)	0.0005
MTHFR C677T MTHFR T677T	MH with 0.5 correction	34.4 0	1.50 (1.01-2.24) 1.38 (0.87-2.22)	0.0473 0.1756
	Inverse Variance with TACC	34.4 0	1.50 (1.01-2.24) 1.34 (0.84-2.16)	0.0473 0.2227
PAI-1 4G/5G PAI-1 4G/4G	MH with 0.5 correction	0 45.4	0.94 (0.65-1.37) 1.90 (0.83-4.33)	0.7555 0.1274
	Inverse Variance with TACC	0 44.7	0.93 (0.64-1.35) 1.85 (0.79-4.32)	0.6854 0.1566
Prothrombin Factor II G20210A	MH with 0.5 correction	36.3	2.07 (0.98-4.39)	0.0580
	Inverse Variance with TACC	37.5	2.03 (0.90-4.60)	0.0885
	Without matched case-control studies (n=10)	38	2.03 (0.90-4.60)	0.0889
VEGFA C634G VEGFA C634C	MH with 0.5 correction	60 58.6	1.25 (0.31-4.99) 1.17 (0.15-9.52)	0.7553 0.8787
	Inverse Variance with TACC	60 56.7	1.25 (0.31-4.99) 1.18 (0.15-9.12)	0.7551 0.8720
VEGF C2578A VEGF C2578C	MH with 0.5 correction	80.4 77.1	1.71 (0.06-50.81) 1.69 (0.07-41.93)	0.7580 0.7514
	Inverse Variance with TACC	68.7 70.5	1.89 (0.04-80.82) 1.83 (0.06-58.05)	0.7407 0.7326

ID – First author	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall
25 - Wang	low	low	low	low	high	low	moderate
192 - Heenkenda	high	low	low	low	high	moderate	high
263 - Heraudeau	low	unsure	low	low	low	low	low
274 - Munoz-Martin	low	unsure	low	low	moderate	low	low
368 - Wang	low	unsure	moderate	low	high	low	moderate
409 - Brad	low	unsure	low	low	low	low	low
467 - Ferroni	low	unsure	low	low	low	low	low
470 - Bianconi	low	unsure	low	low	high	low	moderate
522 - Kovac	low	unsure	low	low	high	low	moderate
524 - Wahba	high	unsure	low	moderate	moderate	moderate	high
528 - Pabinger	low	unsure	low	low	high	low	moderate
624 - Roselli	low	unsure	low	low	high	moderate	moderate
640 - Malaponte	low	unsure	low	moderate	high	low	moderate
785 - Tiedje	low	unsure	low	low	high	low	moderate
786 - Almasi	low	unsure	low	high	high	low	high
831 - de Haas	low	unsure	low	high	high	low	high
849 - Eroglu	high	unsure	low	low	high	low	high
862 - Mandala	low	unsure	low	low	high	low	moderate
913 - Eroglu	high	unsure	low	low	low	moderate	high

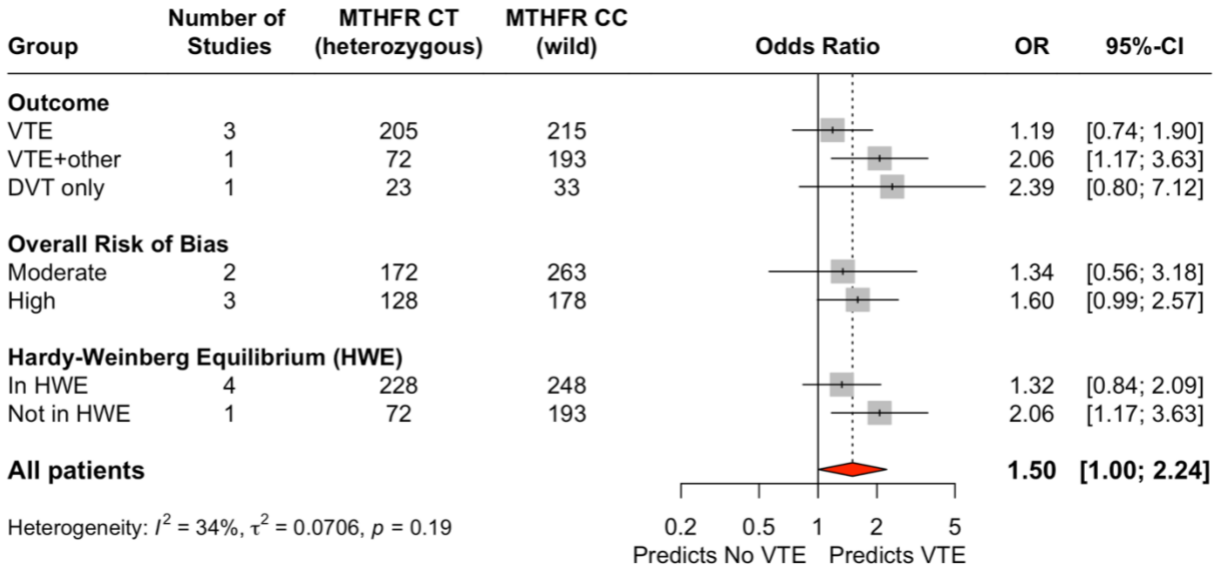
917 - Eroglu	high	unsure	low	low	high	low	high
1035 - Blom	low	moderate	low	low	moderate	low	low
1037 - Kennedy	low	high	low	low	low	low	low
1052 - Corso	moderate	unsure	low	high	high	low	high
1092 - Ravin	low	unsure	low	moderate	high	low	moderate
1129 - Haim	low	unsure	low	low	high	low	moderate
1397 - Labussière	high	unsure	low	high	high	moderate	high
1909 - Ulrych	low	unsure	moderate	low	high	low	moderate
S004 - Arslan	high	unsure	low	low	high	moderate	high
S010 - Crowley	low	low	low	low	low	low	low
S020 - Kodama	low	unsure	low	low	moderate	low	low
S023 – Li	low	unsure	low	low	low	low	low
S029 - Ozkan	moderate	unsure	low	low	high	low	moderate
S035 - Streiff	low	unsure	low	low	high	low	moderate
A1 – Wang	low	low	low	low	moderate	low	low
A2 – Tollefson	low	moderate	low	high	moderate	high	high
A3 - Bhanvandia	low	moderate	low	low	moderate	low	low

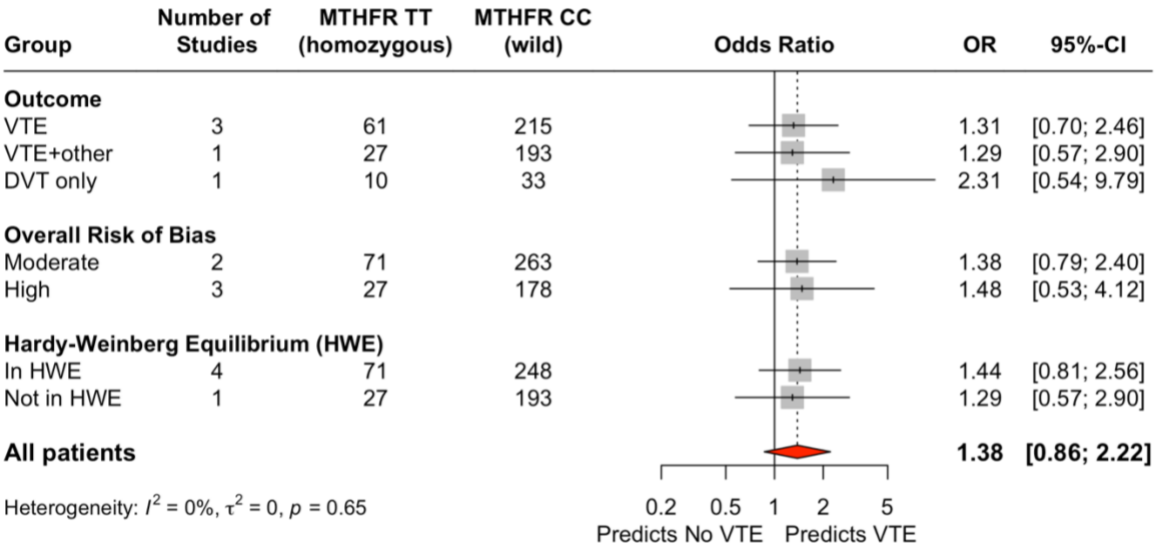
Studies in bold are studies included in the meta-analysis.

Supplemental Figure 1. ROB for each domain of included studies

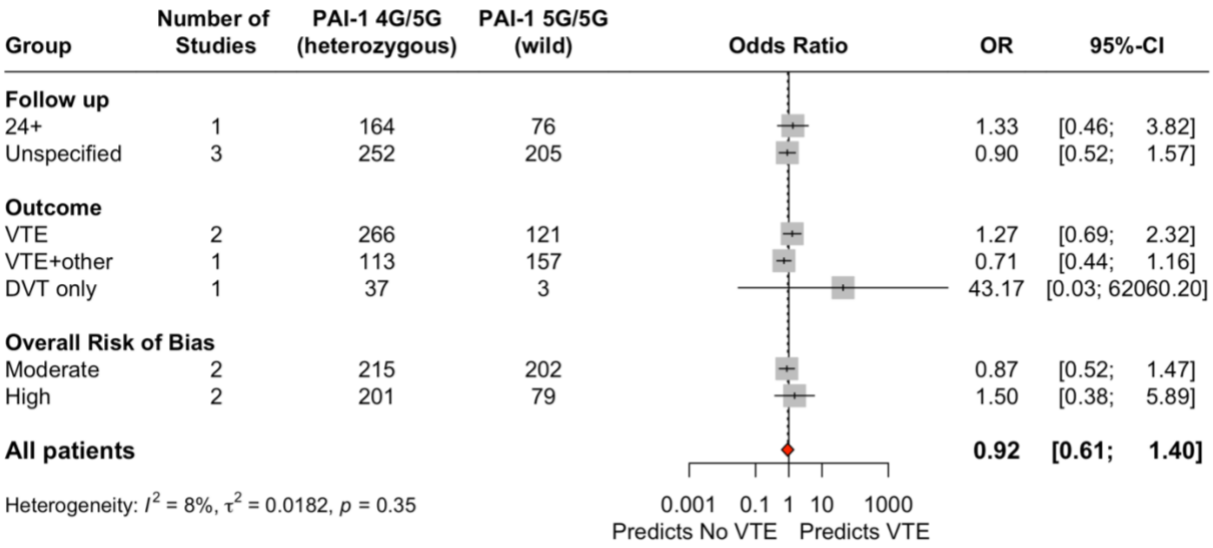


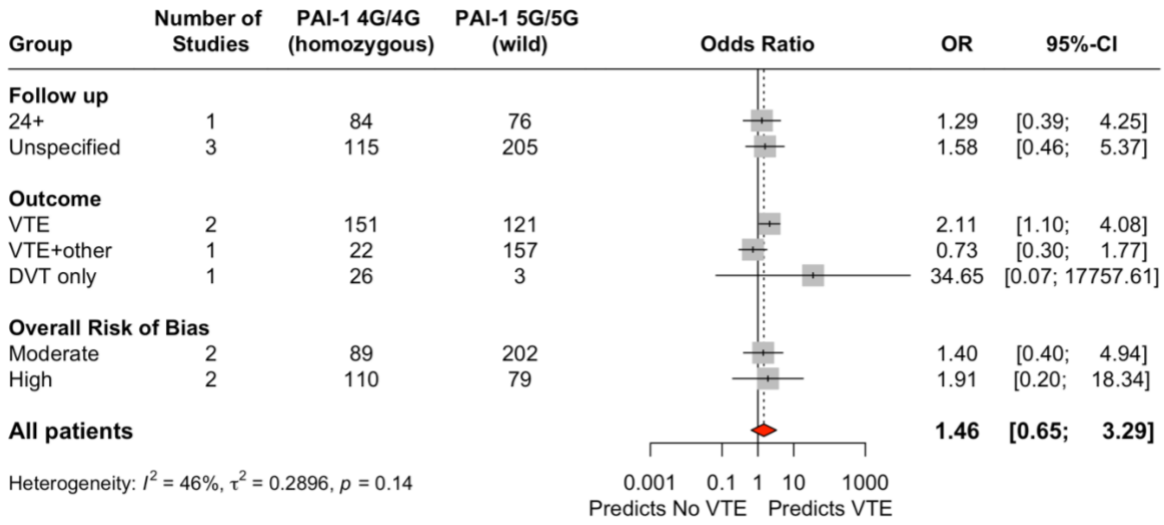
Supplemental Figure 2. Funnel plots of meta-analyses with over 10 studies





Supplemental Figure 3. Forest plot of a) heterozygous and b) homozygous methylenetetrahydrofolate reductase (MTHFR) C677T and VTE risk by subgroup





Supplemental Figure 4. Forest plot of a) heterozygous and b) homozygous plasminogen activator inhibitor-1 (PAI-1) and VTE risk by subgroups

Chapter 4

Circulating Blood Biomarkers and Risk of Venous Thromboembolism in Cancer Patients: A Systematic Review and Meta-Analysis

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Link to article: https://www.thieme-connect.com/products/ejournals/abstract/10.1055/a-2330-1371

Preface to Chapter 4

In this next Chapter, a systematic review and meta-analysis is presented to identify and evaluate candidate circulating blood biomarkers associated with venous thromboembolism (VTE) in patients with cancer. Given the high burden and clinical consequences of cancer-associated VTE, improving risk prediction remains a critical research priority. Current risk prediction models are suboptimal, and the integration of biomarkers may enable a more refined and individualized approach to VTE risk stratification. This systematic review and meta-analysis synthesizes the

available evidence on VTE risk and circulating blood biomarkers measured at distinct clinical timepoints such as, at cancer diagnosis, pre-chemotherapy and preoperatively. The findings presented in this Chapter provide a foundation for future research aimed at advancing personalized thromboprophylaxis strategies using biomarkers and support the importance of considering the timing of biomarker measurement.

4.1 Abstract

Background: Cancer patients have an increased risk of venous thromboembolism (VTE). Currently, the availability of highly discriminatory prediction models for VTE in cancer patients is limited. The implementation of biomarkers in prediction models might lead to refined VTE risk prediction.

Objectives: In this systematic review and meta-analysis, we aimed to evaluate candidate biomarkers and their association with cancer-associated VTE.

Methods: We searched Medline, EMBASE and Cochrane Central for studies that evaluated biomarkers in adult cancer patients from inception to September 2022. We included studies reporting on VTE after a cancer diagnosis with biomarker measurements performed at a defined timepoint. Median/Mean differences (for continuous measures) and Odds Ratios (for dichotomous measures) with 95% confidence intervals were estimated and pooled using random-effects models.

Results: We included 114 studies in the systematic review. Of these, 50 studies were included in the meta-analysis. We identified two biomarkers at cancer diagnosis (factor VIII and time to peak thrombin), three biomarkers pre-chemotherapy (d-dimer, fibrinogen and mean platelet volume) and, one biomarker preoperatively (platelet count) that had significant median or mean differences. Additionally, we found that hemoglobin $<$100g/L and white blood count $>$11 x 10^9/L were significantly associated with future VTE risk only when measured at cancer diagnosis. Pre-chemotherapy neutrophil lymphocyte ratio >3 and preoperative platelet count $\geq$400 x 10^9/L were also found to be associated with future VTE risk.

Conclusions: In conclusion, this study identified nine candidate blood biomarkers that may help in optimizing VTE prediction in cancer patients that should be further explored in future studies.

Keywords: venous thromboembolism, biomarkers, cancer, systematic review, meta-analysis

4.2 Introduction

Venous thromboembolism (VTE) is a common complication associated with cancer. Patients with cancer have a 9-fold increased risk of VTE at 12 months compared to the general population.[1] Despite advances in VTE management, VTE can be life-threatening and lead to considerable health care expenditures, morbidity and mortality.[2–6] In the cancer population, VTE is one of the leading causes of death and has been associated with poor prognosis.[4,7] While prophylactic anticoagulation had been shown to be effective in preventing VTE ,[8–10] it is recommended to target higher risk patients due to the increased risk of bleeding complications with anticoagulants.[11–13] Currently, several VTE risk prediction tools have been developed to identify candidates for primary VTE thromboprophylaxis, some of which include easily measured blood biomarkers.[14–18] However, several limitations regarding the existing scores have been raised including poor overall discriminatory performance and low (or lack of) external validity.[19,20] As such, the availability of reliable and highly discriminatory prediction models for VTE risk assessment in cancer patients is limited, warranting further improvement of VTE risk stratification strategies.

The incorporation of biomarkers in risk assessment models might lead to refined and improved VTE risk prediction, but the identification of the most predictive markers remains to be investigated. To date, d-dimer, hemoglobin, platelet count, white blood cell count and soluble P-selectin remain the most commonly used biomarkers to predict VTE in the cancer population.[14–18] However, some studies report conflicting results with insignificant associations between VTE risk and these biomarkers, thereby questioning their relevance.[19,21,22] Many other candidate blood biomarkers have also been investigated, but the majority have not yet been included in risk scores. The large number of published studies in biomarkers for the prediction of cancer-associated VTE has made it difficult to ascertain which biomarkers are true predictors. Therefore, we performed a systematic review and meta-analysis to evaluate all candidate biomarkers and their association with cancer-associated VTE. By synthesizing existing research, this review seeks to help guide future VTE risk score development and contribute to improving prediction of cancer-associated thrombosis.

4.3 Methods

The data that supports the findings of this study are available within the article and its supplementary files, however, additional files are available from the corresponding author upon reasonable request. Our systematic review was guided by a protocol published in the Open Science Framework Registry (https://doi.org/10.17605/OSF.IO/GQUKW) prior to starting the review. Due to the large number of included studies, we decided *a posteriori* to split the results of the protocol into two manuscripts (genetic biomarkers and blood biomarkers). This helped narrow the topic of each manuscript to ensure applicability, ease of interpretation, and allowed us to include more details in each review. The study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) and updated Preferred Reporting Items for Systematic Reviews guidelines.[23,24]

Search Strategy

A literature search of Medline (Ovid interface), EMBASE (Ovid interface) and Cochrane Central was conducted from inception to September 26th 2022 using search terms relating to VTE, biomarkers and cancer (Supplemental Appendix 1). We also searched the references of included studies for other articles that met eligibility criteria.

Eligibility Criteria

We included observational and interventional studies written in English, French, Chinese or Persian that examined blood biomarkers as a predictor of VTE in human adult patients with cancer. Studies had to report VTE (defined as the occurrence of a first objectively confirmed symptomatic or incidental VTE including upper and lower limbs deep vein thrombosis (DVT), pulmonary embolism (PE) and splanchnic or cerebral vein thrombosis) subsequent to a cancer diagnosis as an outcome with any duration of follow-up. Studies that did not report on DVT or PE and reported exclusively on unusual thrombotic sites (i.e., splanchnic vein thrombosis) were excluded. To be included the study had to report either measures of central tendency or a measure of association (or provided sufficient data for calculation) between blood biomarkers and VTE. Additionally, all blood-based biomarker measurements were included regardless of method of measurement as long as they were definitively and uniformly applied to all patients.

Biomarkers were defined using the National Cancer Institute definition ("a biological molecule found in blood, other body fluids or tissues that is a sign of a normal abnormal process, or of a condition or disease")[25] but we included only biomarkers found in blood in this study. We excluded studies that reported VTE events at the time of biomarker measurement since they were not measures of risk prediction, as well as studies that reported on leukemia or myeloproliferative neoplasms only because they do not reflect the general cancer population. This latter exclusion was not part of the original protocol since the heterogeneity only became evident after the protocol was registered.

Selection Process

Titles and abstracts were independently screened by two reviewers using Covidence Systematic Review Software (Covidence, Melbourne, VIC, Australia). The potentially eligible articles then underwent full-text screening to ascertain the articles meeting the inclusion criteria. Disagreements were resolved by consensus or by a third reviewer. When relevant information to determine eligibility was missing from full-text articles the reviewers attempted to contact the corresponding author for clarification.

To extract the data, a standardized pilot tested form was used. Given the large quantity of studies requiring extraction for both reviews derived from the protocol (n=142; 7 reporting on both biomarkers and thrombophilia genes, 106 reporting on biomarkers only and 29 reporting on thrombophilia genes only), the protocol was amended such that 20% of studies were double extracted by two reviewers while one individual reviewer extracted the data from all studies. We found ~92% agreement between extractors. Data extracted included: study characteristics (e.g., title, authors, year of publication), study design and setting, study population (e.g., sample size, age, sex, eligibility criteria, anticancer treatments), outcome (e.g., VTE definition, length of follow-up), exposure of interest (e.g., biomarker, assay/method of measurement, cut-off, source, timing of measurement) and measures of association with confidence intervals or raw data [e.g., mean, median, odds ratio (OR), hazard ratio, relative risk, 2x2 table]. For studies with multiple reports or overlapping data, the most recent study with the largest sample size was used.

Risk of Bias Assessment

The risk of bias for selected studies was assessed using the Quality in Prognostic Studies (QUIPS) tool which contains six domains: participation, attrition, prognostic factor measurement, outcome measurement, confounding and statistical analysis and reporting. These domains were rated as high, moderate, low or unclear risk of bias and an overall risk of bias score was assigned based on the scoring of the domains. When more than 10 studies were included in the meta-analysis, publication bias was assessed using funnel plots.

Data Synthesis

As studies could report on the same biomarker but in different units, we converted units of measurement whenever possible into one common unit of measurement. A meta-analysis was performed for a particular biomarker when two or more studies measured the biomarkers at defined timepoints during the cancer timeline (e.g., pre-chemotherapy, etc.) and provided either measures of dispersion between groups (VTE and non-VTE) or an OR of VTE using identical cut-offs. The biomarkers that could not be meta-analyzed were narratively summarized in a supplemental table. We conducted two types of random-effects meta-analyses: meta-analysis of median or mean differences (for continuous data)[26] and DerSimonian and Laird generic inverse variance meta-analysis (for cut-off/dichotomous data).[27] When the majority of studies reported the median, a meta-analysis of median differences was performed whereas a meta-analysis of mean differences was performed when the majority of studies reported the mean. Additionally, for the meta-analyses of median differences, we used the quantile matching estimation approach to estimate the difference of medians and, for the meta-analysis of mean differences, we used the method for unknown non-normal distributions to estimate the means. These methods were selected based on the simulation results and recommendations made by McGrath et al[28] and Cai et al[29], which demonstrated less bias with these methods. Heterogeneity among studies was assessed using the I^2 statistic and characterized as non-important (I^2<30%), moderate (I^2=30%-75%) and considerable (I^2>75%). We performed subgroup and sensitivity analyses to explore potential differences in biomarkers when there are many included studies and when considerable heterogeneity was present. We assessed the certainty of evidence using the grading of recommendations assessment, development, and evaluation (GRADE) approach.[30] We used a significance level of 0.05. All analyses were conducted in R version 4.2.3 (R Core Team and R Foundation for Statistical Computing, Vienna, Austria) and RStudio version 2023.06.1 (Posit

software, PBC, Vienna, Austria) with the help of the *metamedian* version 1.0.0 and *meta* R packages.[31,32]

4.4 Results

A total of 5529 articles were identified using our search strategy, of which 4274 remained after removal of duplicates. After title and abstract screening, we included 841 studies for full-text screening. Seventy-seven studies met the eligibility criteria and were included in the review, along with an additional 36 studies identified during reference list screening (Figure 1). Many of these latter studies had a primary goal of assessing risk prediction tools or risk factors, and therefore lacked biomarker wording. In total, there were 566 different biomarker measurements extracted from these studies, of which 182 biomarker measurements were included in the meta-analysis.

Key study characteristics and individual biomarker estimates of all studies are shown in Table 1 and Supplemental Tables 1-6. From the 113 studies included,[18,33–113,22,114–143] only 50 provided biomarker estimates allowing for meta-analysis.[22,33–38,40,44–46,49,50,55,57,59,63,64,72–74,76,77,80,81,83–85,87,92,97,98,100,103–105,107,110,120,121,124–126,132,133,136,137,140–142] The majority of these studies were cohort studies, of which 28 were prospective and 19 were retrospective. The remaining 3 studies were nested case-control studies. Fifteen studies included mixed cancer types while the others included patients with specific cancer types, including lung (n=5), gynecologic (n=4), colorectal (n=4), multiple myeloma (n=3), ovarian (n=3), pancreas (n=3), brain (n=2), breast (n=2), stomach (n=2), lymphoma (n=2), gastrointestinal (n=1), genitourinary (n=1), gynecologic or breast (n=1), head and neck (n=1), and liver (n=1). Biomarker measurements were carried out either preoperatively (n=18), at time of cancer diagnosis (n=15) or prechemotherapy (n=20) (three studies reported both preoperative and prechemotherapy measurements). Forty-three studies reported on overall VTE as the outcome whereas five and two studies reported only on either DVT or PE only, respectively. The characteristics of studies that contributed to the meta-analyses are summarized by biomarker in Table 1.

From the 50 studies included in the meta-analyses, 25 studies had a low risk of bias, 20 studies had a moderate risk of bias and 5 studies had a high risk of bias. The number of low, moderate and high risk of bias studies in each meta-analysis is described in Figure 2. Studies with a moderate or high risk of bias were likely to have bias due to confounding. Information on

follow-up was missing in many studies affecting our ability to determine if these studies had attrition bias (Supplemental Table 7).

In total, 34 studies[33,35,37,38,40,44,46,49,50,57,59,63,64,72,73,80,81,83–85,87,97,98,103,104,110,120,124,126,132,133,136,137,141] provided the necessary measures to estimate pooled median or mean differences for 10, 8 and 17 different biomarkers measured at cancer diagnosis, pre-chemotherapy and preoperatively, respectively (Table 2). Compared to cancer patients who did not experience VTE, those who experienced VTE events had significantly higher factor VIII activity [median difference: 31.50 % activity (95% CI: 11.55-51.45), I^2=0%] and lower time to peak thrombin [median difference: -1.39 minutes (95% CI: -2.27 to -0.51), I^2=0%] at the time of cancer diagnosis (Table 2). Cancer patients who experienced VTE events also had significantly higher pre-chemotherapy D-dimer levels [median difference: 1.79 ug/mL (95% CI: 1.12-2.46), I^2=0%, Supplemental Figure 1] and fibrinogen levels [mean difference: 0.81 g/L (95% CI: 0.31-1.32), I^2=0%] and, significantly lower pre-chemotherapy mean platelet volume levels [mean difference: -0.39 fL (95% CI: -0.73 to -0.05), I^2=0%] compared to patients who did not develop VTE (Table 2). In cancer patients undergoing surgery, those who experienced VTE after surgery had significantly higher preoperative platelet count [mean difference: 17.21 x 10^9/L (95% CI: 1.74-32.68), I^2=41%] compared to patients who did not develop VTE (Table 2).

Only a select few studies (n=21)[22,34,36,45,46,50,55,74,76,77,84,92,100,104,105,107,121,125,126,140,142] reported on *a priori* or predefined cut-off values and provided the necessary data to calculate pooled ORs of specific dichotomous biomarker cut-offs at defined timepoints. Many studies used cut-off values derived from their individual studies, resulting in the inability to calculate pooled effect estimates. In the biomarkers that were meta-analyzed dichotomously, the results showed that hemoglobin levels $<$ 100 g/L was significantly associated with future VTE risk when measured at the time of cancer diagnosis [OR: 1.86 (95%CI: 1.21-2.86), I^2=0%], but not when measured pre-chemotherapy or preoperatively (Table 3 and Figure 3). Similarly, white blood count levels $>$ 11 x 10^9/L was also associated with an increased risk of VTE when measured at the time of cancer diagnosis [OR: 1.67 (95%CI: 1.06-2.62), I^2=2%] but not when measured pre-chemotherapy (Table 3 and Figure 3). In addition, patients with cancer and pre-chemotherapy Neutrophil Lymphocyte Ratios (NLR) $\geq$ 3 had significantly increased odds of VTE compared to cancer patients with ratios below 3 ([OR: 1.47 (95%CI: 1.01-2.13), I^2=0%, Table 3]. At cancer diagnosis, this ratio cut-off was not significantly associated with VTE risk however, moderate

heterogeneity was observed. Platelet count $\geq$ 350 x 10^9/L measured at the time of cancer diagnosis or pre-chemotherapy was not associated with VTE risk (Table 3 & Figure 3), however, the risk of VTE was significantly increased when preoperative platelet count exceeded the 400 x 10^9/L cut-off [OR: 1.97 (95%CI: 1.58-2.46), I^2=0%, Table 3].

We conducted sensitivity analyses excluding studies with long durations of follow-up (> 12 months) (Supplemental Tables 8-9) and excluding studies that included asymptomatic VTE via screening (Supplemental Tables 10-11), and they yielded similar results. In addition, since the Khorana score is not recommended in patients with brain cancer or multiple myeloma given their underrepresentation in the original derivation cohort,[14] we performed a third sensitivity analysis excluding studies conducted solely in brain or multiple myeloma cancer patients. Similar results were also observed (Supplemental Table 12).

4.5 Discussion

In this meta-analysis, we identified two biomarkers at cancer diagnosis (factor VIII and time to peak thrombin), three biomarkers pre-chemotherapy (d-dimer, fibrinogen and mean platelet volume) and, one biomarker preoperatively (platelet count) that were significantly altered in cancer patients who developed VTE compared to those that did not develop VTE according to the median/mean differences. Additionally, we found that hemoglobin $<$ 100 g/L and white blood count $>$ 11 x 10^9/L were significantly associated with future VTE risk only when measured at cancer diagnosis whereas platelet count $\geq$ 350 x 10^9/L showed no association. Pre-chemotherapy NLR >3 and preoperative platelet count $\geq$ 400 x 10^9/L were also found to be associated with future VTE risk. To our knowledge, this is the first systematic review with meta-analyses evaluating the association between multiple biomarkers and VTE risk in patients with cancer.

Blood hemostasis and clot formation is controlled by various enzymes, factors and proteins.[144] Therefore, it should be no surprise that the incidence of VTE is therefore heterogenous among patients with certain biomarkers. In this study, cancer patients who developed subsequent VTE had significantly higher or lower levels of certain biomarkers that differed by timing of measurement. Of note, the significant difference in pre-chemotherapy fibrinogen levels should be interpreted with caution due to the low number of patients, low event rate and the inclusion of female-only studies. Nonetheless, the findings of increased VTE risk in

patients with elevated or decreased biomarker levels we report in this paper are aligned with other studies evaluating the same biomarkers levels at the time of VTE in cancer patients,[145–148] as predictors of first symptomatic provoked VTE,[149,150] and as risk factors in the general population.[151–153] This supports that certain biomarkers could play a role in the prediction of VTE. Future research should investigate these biomarkers and assess their performance in risk prediction models at pre-defined timepoints. From the identified biomarkers, D-dimer has previously been integrated in VTE risk models in newly diagnosed cancer patients[18,154] given its strong association with future VTE risk. However, since the results mainly derive from the same cohort and in newly diagnosed cancer patients,[18,154] D-dimer should be further investigated in future research along with the other biomarkers. Notably, it is important to also mention that some of these biomarkers are not routinely available in clinical practice or measured for VTE prediction in cancer patients. If confirmed, these biomarkers may represent important predictors to measure in practice. To effectively integrate the use of biomarkers for VTE prediction, efforts should be made to unify test methods and units reported.

Our study also evaluated the predictive ability of several commonly used blood tests for VTE in cancer patients. Three particular biomarkers that were meta-analyzed are the complete blood count (CBC) components as part of the Khorana score including hemoglobin < 100 g/L, platelet count $\geq 350 \times 10^9$/L and white blood count $> 11 \times 10^9$/L.[14] The Khorana score is currently the most widely known and validated risk stratification tool to stratify the risk of VTE in ambulatory cancer patients initiating chemotherapy. However, recent studies have shown that the discriminatory performance of the Khorana score is suboptimal with modest proportions of patients with VTE assigned as high-risk, and there was inconsistency across cancer types.[19,20,155,156] In our study, we did not find significant associations between the three pre-chemotherapy CBC components and VTE risk, thereby questioning the relevance of these cut-offs as predictors. Other prospective cohort studies have reported similar findings based on multivariate analyses.[19,21,122] It is also possible that the insignificant associations we observed are due to the dichotomization of biomarker levels (instead of using continuous values) which leads to a loss of information.[157] However, hemoglobin levels < 100 g/L and white blood count levels $> 11 \times 10^9$/L measured at cancer diagnosis were found significantly associated with subsequent VTE risk. This suggests that these cut-offs may be better used at the time of cancer diagnosis in patients who have not yet received anticancer therapy. In some, pre-chemotherapy may coincide

with the time of cancer diagnosis however, for others, it may indicate starting a new chemotherapy regimen after previous rounds of chemotherapy treatment. In these latter patients, blood counts may not predict VTE given that chemotherapy agents could have affected blood counts.[158–160] Furthermore, another biomarker that we evaluated was NLR>3. We found an increased risk of VTE in cancer patients with NLR>3 pre-chemotherapy and at cancer diagnosis, yet, statistically significant only for pre-chemotherapy. In both meta-analyses, only two studies were included, suggesting this association should be explored further. There is growing evidence that there is a link between inflammation and increased VTE risk,[161] supporting the utility of inflammation markers such as NLR to predict VTE.

It is well known that surgery is a major risk factor for VTE.[1] In terms of patients undergoing oncologic surgery, we meta-analyzed biomarker levels measured preoperatively to determine if any may aid in the prediction of postoperative VTE. One particular biomarker, platelet count, showed promise in predicting postoperative VTE events in cancer patients. We found significantly higher preoperative platelet count in patients who developed postoperative VTE events compared to patients who did not develop postoperative VTE. Additionally, we also reported an increased VTE risk in cancer patients with preoperative platelet count $\geq 400 \times 10^9$/L. A previous systematic review and meta-analysis investigating platelet count and thrombosis in cancer reported similar results.[162] These findings provide evidence that having a high platelet count coupled with surgery may increase the risk of VTE in cancer patients. This same effect may not be seen in cancer patients with elevated platelet counts at cancer diagnosis or pre-chemotherapy as chemotherapy agents can cause a reduction in platelet count levels which may exert a protective effect.[158,163]

There were some limitations in this study. First, we performed meta-analyses on biomarkers when two or more studies provided the necessary information. This approach led us to focus on biomarkers that were consistently analyzed in multiple articles and ignore potentially more novel or unpopular biomarkers that have not yet been widely reported. As such, our ability to make pooled inferences for less commonly reported biomarkers was limited. Second, the patient characteristics and definition of VTE varied across studies, which caused some heterogeneity in our pooled estimates and may limit the generalizability of our findings to certain patient populations. Most studies had a VTE definition of objectively diagnosed symptomatic or incidental VTE, however some studies, mainly in the perioperative setting, also included

asymptomatic VTE events (identified via screening) which may influence results. Also, although we pooled studies with similar timing of biomarker measurements, there may have been some variations in terms of when blood was collected (i.e., blood measured preoperatively could have been measured the day of surgery or days prior to the procedure). Third, we pooled unadjusted estimates, which could have led to residual confounding. However, we chose to pool unadjusted estimates because the included studies did not determine the confounders a priori and/or had evidence of overadjustment. Lastly, it is possible that in some patients, D-dimer served as a diagnostic biomarker reflecting a silent or subclinical VTE event that later became clinically detected cases. However, we tried to minimize this by excluding studies with VTE events at the time of biomarker measurement or inclusion and focusing on primarily prediction studies with follow-up periods ranging from one week to a little over two years. Six studies[59,63,64,72,98,132] included in the D-dimer meta-analyses also either screened all patients with diagnostic tests or excluded patients with any evidence of VTE at the start of follow-up. In contrast, our study has important strengths. For the majority of our meta-analyses, we attained a large sample of cancer patients and VTE events, providing good precision and sufficient statistical power in the analyses. Our statistical analyses were also rigorous and we performed meta-analyses for numerous biomarkers. Additionally, we excluded articles reporting VTE at the time of biomarker measurement which ensured biomarkers to be measures of risk of VTE, and that they were not confounded by the effects of an existing VTE event. Similarly, our strategy to pool the estimates by the timing of measurements ensured that the biomarkers were not confounded by treatment effects and improved generalizability of the findings.

Our study has important implications for future studies aiming to utilize biomarkers or construct models for VTE risk prediction in cancer. In this systematic review and meta-analysis, we comprehensively reviewed and meta-analyzed various biomarkers that were evaluated in the literature and highlighted several biomarkers that may be useful in the prediction of VTE in cancer patients. The identification of promising biomarkers in this review provides important insights for future research efforts aiming to improve VTE prediction in patients with cancer. The inclusion of some of these biomarkers in risk assessment models may help in the identification of cancer patients at high risk of VTE and therefore, candidates for thromboprophylaxis.

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Table 1. Characteristics of studies that contributed to the meta-analysis (MA) by biomarker

Biomarker	Contributed to MA				N of studies not contributing to MA
	Timing of measurement	N of studies	Cancer Types[c]	Outcome[c]	
Activated Partial Thromboplastin time	Preoperative	4	Gynecologic (n=2), Brain, Stomach	VTE (n=3), DVT	5
Albumin	Preoperative	3	Colorectal, Ovarian, Stomach	VTE (n=2), DVT	6
C-reactive protein	Preoperative	4	Brain, Genito-urinary, Gynecologic, Stomach	VTE (n=3), PE	4
D-dimer	At cancer diagnosis	2	Various or Pancreas	VTE (n=2)	28
	Pre-chemotherapy	5	Various (n=3) or Lung, Ovarian	VTE (n=5)	
	Preoperative	6	Gynecologic (n=2), Brain, Breast, Lung, Stomach	VTE (n=3), DVT (n=2), PE	
Factor VIII activity	At cancer diagnosis	2	Various or Pancreas	VTE (n=2)	6
Fibrinogen	At cancer diagnosis	2	Lymphoma, Pancreas	VTE (n=2)	6
	Pre-chemotherapy	3	Breast, Ovarian (n=2)	VTE (n=3)	
	Preoperative	5	Brain (n=2), Breast, Ovarian (n=2)	DVT (n=3), VTE, PE	
Hematocrit	Pre-chemotherapy	2	Breast, Ovarian	DVT (n=2)	--

Hemoglobin[a]	At cancer diagnosis	5	Various or Pancreas (n=2), Lymphoma	VTE (n=5)	9
	Pre-chemotherapy	6	Various (n=2) or Ovarian (n=2), Myeloma, Pancreas	VTE (n=5), DVT	
	Preoperative	7	Breast (n=2), Brain, Colorectal, Gynecologic, Ovarian, Stomach,	VTE (n=3), DVT (n=3), PE	
Hemoglobin[b]	At cancer diagnosis	4	Various or Colorectal, Liver, Pancreas	VTE (n=4)	
	Pre-chemotherapy	10	Various (n=3) or Lung (n=2), Myeloma (n=2), Colorectal, Lymphoma, Pancreas	VTE (n=9), DVT	
Lymphocyte Count	Preoperative	3	Gastric, Gynecologic, Head and Neck	VTE (n=3)	3
Mean Platelet Volume	Pre-chemotherapy	2	Various (n=2)	VTE (n=2)	2
Neutrophil Count	At cancer diagnosis	2	Gastrointestinal, Gynecologic	VTE (n=2)	6
	Preoperative	3	Brain, Gynecologic, Stomach	VTE (n=2), PE	
Neutrophil Lymphocyte Ratio	At cancer diagnosis	2	Gastric, Lymphoma	VTE (n=2)	2
	Pre-chemotherapy	2	Various or Pancreas	VTE (n=2)	
Peak thrombin	At cancer diagnosis	3	Various or Lung, Pancreas,	VTE (n=3)	5
Platelet Count[a]	At cancer diagnosis	4	Various or Gynecologic, Lymphoma, Pancreas	VTE (n=4)	17
	Pre-chemotherapy	6	Various (n=2) or Gynecologic, Myeloma, Ovarian, Pancreas	VTE (n=5), DVT	

	Preoperative	10	Gynecologic (n=4), Brain (n=2), Breast, Colorectal, Head and neck, Stomach	VTE (n=5), PE (n=2), DVT (n=3)	
Platelet Count[b]	At cancer diagnosis	5	Various or Colorectal, Gynecologic, Liver, Pancreas	VTE (n=5)	
	Pre-chemotherapy	8	Various (n=3) or Lung (n=2), Colorectal, Lymphoma, Myeloma	VTE (n=7), DVT	
	Preoperative	2	Various or Colorectal	VTE (n=2)	
Platelet Lymphocyte Ratio	Pre-chemotherapy	2	Various or Pancreas	VTE (n=2)	5
Prothrombin time - ratio	Preoperative	2	Brain, Gynecologic	VTE, PE	3
Prothrombin time - sec	Preoperative	2	Brain, Ovarian	VTE, DVT	
Prothrombin time - %	Preoperative	2	Brain, Stomach	VTE, DVT	
Red blood cell aggregate low shear	Preoperative	2	Breast, Gynecologic	VTE, DVT	--
Red blood cell aggregate stasis	Preoperative	2	Breast, Gynecologic	VTE, DVT	--
Soluble P-selectin	At cancer diagnosis	2	Various or Pancreas	VTE (n=2)	4
	Pre-chemotherapy	2	Various (n=2)	VTE (n=2)	
Time to peak thrombin	At cancer diagnosis	2	Various or Lung	VTE (n=2)	3

White Blood Count[a]	At cancer diagnosis	5	Various or Gynecologic, Gastrointestinal, Lymphoma, Pancreas	VTE (n=5)	11
	Pre-chemotherapy	5	Various (n=2) or Ovarian (n=2), Pancreas	VTE (n=4), DVT	
	Preoperative	8	Gynecologic (n=2), Brain (n=2), Breast, Colorectal, Head and Neck, Stomach	VTE (n=3), DVT (n=4), PE	
White Blood Count[b]	At cancer diagnosis	4	Various or Colorectal, Gynecologic, Liver	VTE (n=4)	
	Pre-chemotherapy	9	Various (n=4) or Lung (n=2), Colorectal, Myeloma, Ovarian	VTE (n=8), DVT	

Abbreviations: DVT=Deep Vein Thrombosis, MA=Meta-analysis, PE=Pulmonary Embolism, VTE=Venous Thromboembolism

[a]Included in the meta-analysis of median/mean differences

[b]Included in the generic inverse variance DerSimonian Laird meta-analysis

[c]No number is provided in parentheses when only one study reported on the cancer type or VTE outcome

Table 2. Median or mean differences in biomarker levels between VTE and non-VTE patients when measured at cancer diagnosis, pre-chemotherapy or preoperatively

Biomarkers	N of studies	Sample size	VTE	I^2, %	Median difference/ **Mean difference**	*P-value*	**Certainty of evidence (GRADE)[a]**
AT CANCER DIAGNOSIS							
D-dimer (ug/mL)[b]	2	1726	154	60.4	0.75 (-0.23-1.72)	*0.1326*	⊕⊕⊕⊖ **Moderate**[g]
Factor VIII (% activity)	2	881	71	0	31.50 (11.55-51.45)	*0.0020*	⊕⊕⊕⊕ **High**
Fibrinogen (g/L)[c]	2	747	78	52.8	0.05 (-0.64-0.73)	*0.8983*	⊕⊕⊕⊖ **Moderate**[h]
Hemoglobin (g/L)	4	2544	236	51.1	-3.48 (-8.69-1.73)	*0.1900*	⊕⊕⊕⊕ **High**
Neutrophil Count ($x10^9$/L)	2	151	26	0	0.80 (-1.22-2.82)	*0.4400*	⊕⊕⊕⊖ **Moderate**[i]
Peak thrombin (nM)	3	1201	98	0	29.82 (-1.71-61.34)	*0.0638*	⊕⊕⊕⊕ **High**
Platelet Count ($x10^9$/L)	4	2551	239	65.2	-0.82 (-41.68-40.04)	*0.9687*	⊕⊕⊕⊖ **Moderate**[g]
Soluble P-Selectin[d]	2	728	53	0	4.02 (-2.85-10.89)	*0.2513*	⊕⊕⊕⊕ **High**
Time to peak thrombin (min)	2	1160	89	0	-1.39 (-2.27--0.51)	*0.0020*	⊕⊕⊕⊖ **Moderate**[h]
White Blood Count ($x10^9$/L)	5	2583	249	19.1	0.47 (-0.14-1.08)	*0.1314*	⊕⊕⊕⊕ **High**
PRE-CHEMOTHERAPY							
D-dimer (ug/mL)[b]	5	528	59	0	1.79 (1.12-2.46)	*<0.0001*	⊕⊕⊕⊖ **Moderate**[h]
Fibrinogen (g/L)[e]	3	141	15	0	**0.81 (0.31-1.32)**	*0.0016*	⊕⊕⊖⊖ **Low**[h,i]

Hematocrit (%)	2	84	10	42.6	**-0.25 (-4.59-4.09)**	*0.9096*	⊕⊕⊖⊖ **Low**[h,i]
Hemoglobin (g/L)	6	1075	16 6	0	**-0.12 (-1.14-0.90)**	*0.8170*	⊕⊕⊕⊖ **Moderate**[h]
Mean Platelet Volume (fL)	2	678	50	0	-0.39 (-0.73--0.05)	*0.0226*	⊕⊕⊕⊕ **High**
Platelet Count (x10^9/L)	6	1075	16 6	17.3	10.63 (-9.60-30.87)	*0.3031*	⊕⊕⊕⊖ **Moderate**[h]
Soluble P-Selectin[d]	2	233	26	0	6.67 (-3.83-17.16)	*0.2131*	⊕⊕⊕⊖ **Moderate**[i]
White Blood Count (x10^9/L)	5	964	14 5	0	**0.03 (-0.41-0.47)**	*0.8803*	⊕⊕⊕⊕ **High**
PREOPERATIVE							
Activated Partial Thromboplastin Time (sec)	4	926	11 6	39.2	-0.73 (-2.34-0.89)	*0.3800*	⊕⊕⊕⊕ **High**
Alanine transaminase (IU/L)	2	618	78	0	1.09 (-4.66-6.84)	*0.7105*	⊕⊕⊕⊕ **High**
Albumin (g/L)	3	614	47	0	-1.68 (-3.38-0.02)	*0.0530*	⊕⊕⊖⊖ **Low**[h,i]
C-Reactive Protein (mg/L)	4	490	66	0	0.01 (-0.06-0.08)	*0.7800*	⊕⊕⊕⊖ **Moderate**[h]
D-dimer (ug/mL)	6	1091	12 5	26.9	0.13 (-0.04-0.30)	*0.1386*	⊕⊕⊖⊖ **Low**[h,j]
Quantitative latex-enhanced immunoassay[b]	1	234	15	NA	0.76 (-0.14-1.66)	*0.0964*	⊕⊕⊖⊖ **Very Low**[h,i]
Latex photometric immunoassay	1	75	21	NA	0.30 (-0.37-0.97)	*0.3782*	⊕⊕⊖⊖ **Very Low**[h,i]
Not stated	4	782	89	2.4	0.04 (-0.04-0.12)	*0.3546*	⊕⊕⊖⊖ **Low**[h,j]
Fibrinogen (g/L)[f]	5	914	13 9	0	**0.14 (-0.02-0.30)**	*0.0902*	⊕⊕⊕⊖ **Moderate**[h]

Hemoglobin (g/L)	7	1452	163	63.5	-0.69 (-6.34-4.96)	*0.8106*	⊕⊕⊖⊖ **Low**[g,h]
Lymphocyte Count ($x10^9$/L)	3	1048	65	69.9	-0.43 (-0.88-0.03)	*0.0647*	⊕⊕⊕⊖ **Moderate**[g]
Neutrophil Count ($x10^9$/L)	3	842	93	0	0.05 (-0.56-0.66)	*0.8685*	⊕⊕⊕⊕ **High**
Platelet Count ($x10^9$/L)	10	2515	265	41.4	**17.21 (1.74-32.68)**	*0.0292*	⊕⊕⊕⊖ **Moderate**[h]
Prothrombin time (ratio)	2	175	55	0	-0.01 (-0.04-0.02)	*0.4069*	⊕⊕⊕⊖ **Moderate**[h]
Prothrombin time (sec)	2	233	17	0	**-0.20 (-0.76-0.36)**	*0.4802*	⊕⊕⊕⊖ **Moderate**[i]
Prothrombin time (%)	2	618	78	0	-5.97 (-12.27-0.34)	*0.0635*	⊕⊕⊕⊕ **High**
Red blood cell aggregate low shear	2	307	33	76.0	4.11 (-1.72-9.93)	*0.1670*	⊕⊖⊖⊖ **Very Low**[g,h,i]
Red blood cell aggregate stasis	2	307	33	0	1.76 (-0.21-3.72)	*0.0798*	⊕⊕⊖⊖ **Low**[h,i]
Thrombin time (sec)	2	725	90	0	0.00 (-0.30-0.30)	*1.0000*	⊕⊕⊕⊕ **High**
White Blood Count ($x10^9$/L)	8	2175	222	0	0.01 (-0.35-0.37)	*0.9456*	⊕⊕⊕⊖ **Moderate**[h]

Abbreviations: VTE=Venous Thromboembolism

[a]High certainty of evidence is characterised by four positive symbols (⊕⊕⊕⊕) but, for each downgrade in certainty, a positive symbol was replaced with a negative symbol (⊖)

[b]D-dimer levels for the included studies were measured via quantitative latex-enhanced immunoturbidimetric immunoassay (cut-off for the assay: 0.5 ug/mL).

[c]Levels measured using the Clauss method in one study and method of measurement was not stated in the other.

[d]Soluble P-selectin measured using human sP-selectin Immunoassay from R&D Systems Inc.

[e]All three studies measured fibrinogen using the Clauss method.

[f]Levels measured using the Clauss method in two studies and method of measurement not stated in the others.

[g]Due to inconsistency; the measure of heterogeneity (I^2) is large for the number of included studies

[h]Due to risk of bias; the majority of studies have moderate to high risk of bias

[i]Due to imprecision; low event rate or sample size

[j]The included studies did not all specify the method of measurement of D-dimer (indirectness of exposure)

Table 3. The odds ratios (OR) of dichotomous biomarker cut-offs to predict VTE in cancer patients

Biomarkers	Cut-off[b]	N of studies	Sample size	VTE	I^2, %	Pooled OR	*P-value*	Certainty of evidence (GRADE)[a]
AT CANCER DIAGNOSIS								
Hemoglobin (g/L)	< 100	4	1576	252	0	1.86 (1.21-2.86)	*0.0048*	⊕⊕⊕⊕ **High**
Neutrophil Lymphocyte Ratio	≥ 3	2	818	82	67.1	1.61 (0.55-4.74)	*0.3904*	⊕⊕⊖⊖ **Low**[c,d]
Platelet Count (x10^9/L)	≥ 350	5	1695	268	57.9	1.09 (0.59-2.00)	*0.7797*	⊕⊕⊕⊖ **Moderate**[c]
White Blood Count (x10^9/L)	> 11	4	1025	164	2.2	1.67 (1.06-2.62)	*0.0272*	⊕⊕⊕⊕ **High**
PRE-CHEMOTHERAPY								
Hemoglobin (g/L)	< 100	10	7134	618	45.2	1.14 (0.76-1.71)	*0.5168*	⊕⊕⊕⊕ **High**
Neutrophil Lymphocyte Ratio	≥ 3	2	1236	141	0	1.47 (1.01-2.13)	*0.0421*	⊕⊕⊕⊕ **High**
Platelet Count (x10^9/L)	≥ 350	8	6508	519	29.1	0.94 (0.69-1.29)	*0.7190*	⊕⊕⊕⊕ **High**
Platelet Lymphocyte Ratio	≥ 260	2	1236	141	22.1	1.36 (0.79-2.35)	*0.2742*	⊕⊕⊕⊕ **High**
White Blood Count (x10^9/L)	> 11	9	10911	635	55.1	1.20 (0.80-1.78)	*0.3799*	⊕⊕⊕⊖ **Moderate**[c]
PREOPERATIVE								
Hemoglobin (g/L)	< 100	2	800	73	28.3	0.99 (0.52-1.89)	*0.9816*	⊕⊕⊕⊕ **High**
Platelet Count (x10^9/L)	≥ 400	2	45056	731	0	1.97 (1.58-2.46)	*<0.0001*	⊕⊕⊕⊕ **High**

Abbreviations: OR=Odds Ratio, VTE=Venous Thromboembolism

[a]High certainty of evidence is characterised by four positive symbols (⊕⊕⊕⊕) but, for each downgrade in certainty, a positive symbol was replaced with a negative symbol (⊖)

[b]Some studies used $\geq$ *or* $\leq$ instead of $>$ and $<$ for hemoglobin and white blood count

[c]Due to inconsistency; the measure of heterogeneity (I^2) is large for the number of included studies

[d]Due to risk of bias; the majority of studies have moderate to high risk of bias

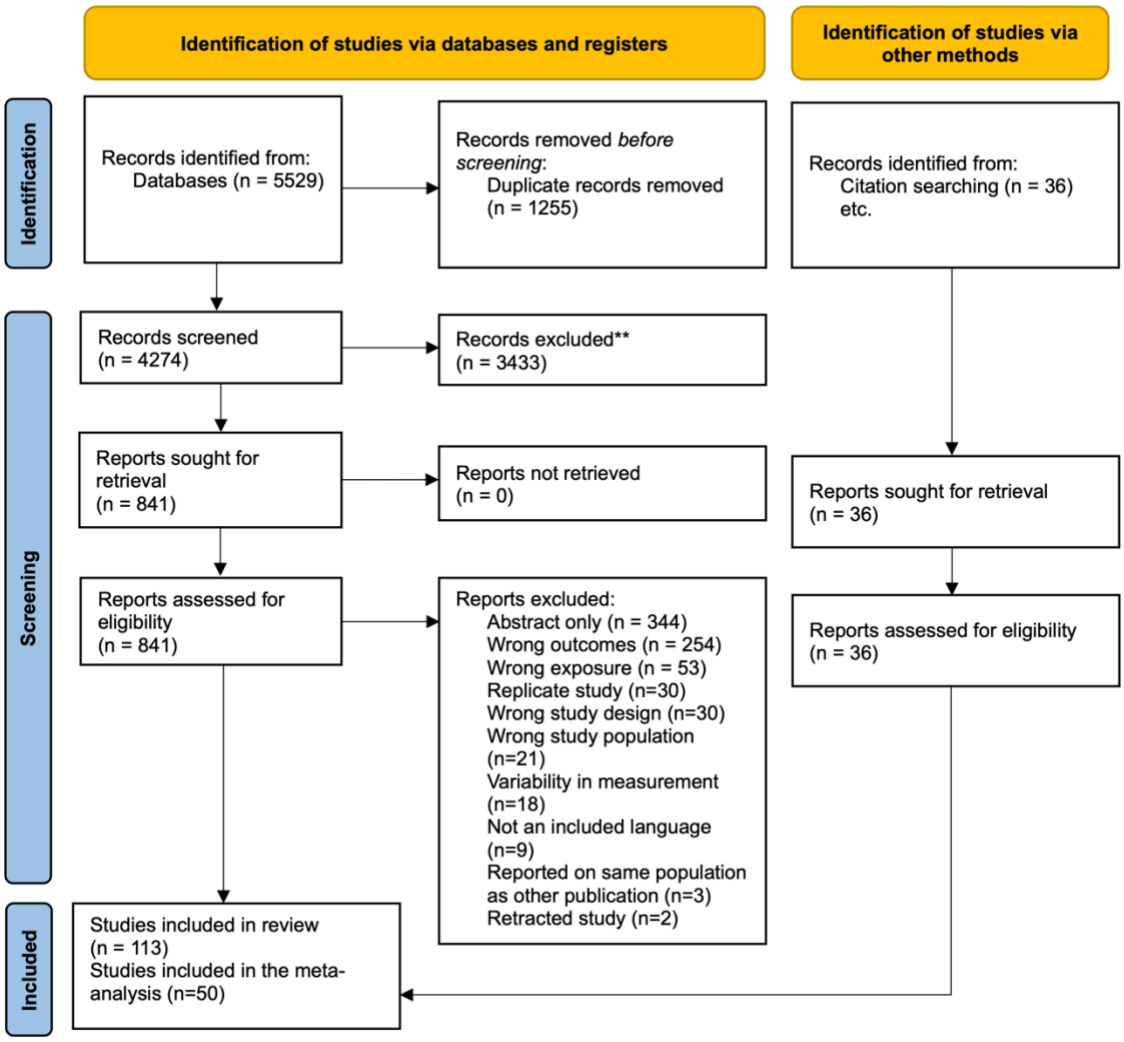


Figure 1. PRISMA flow diagram

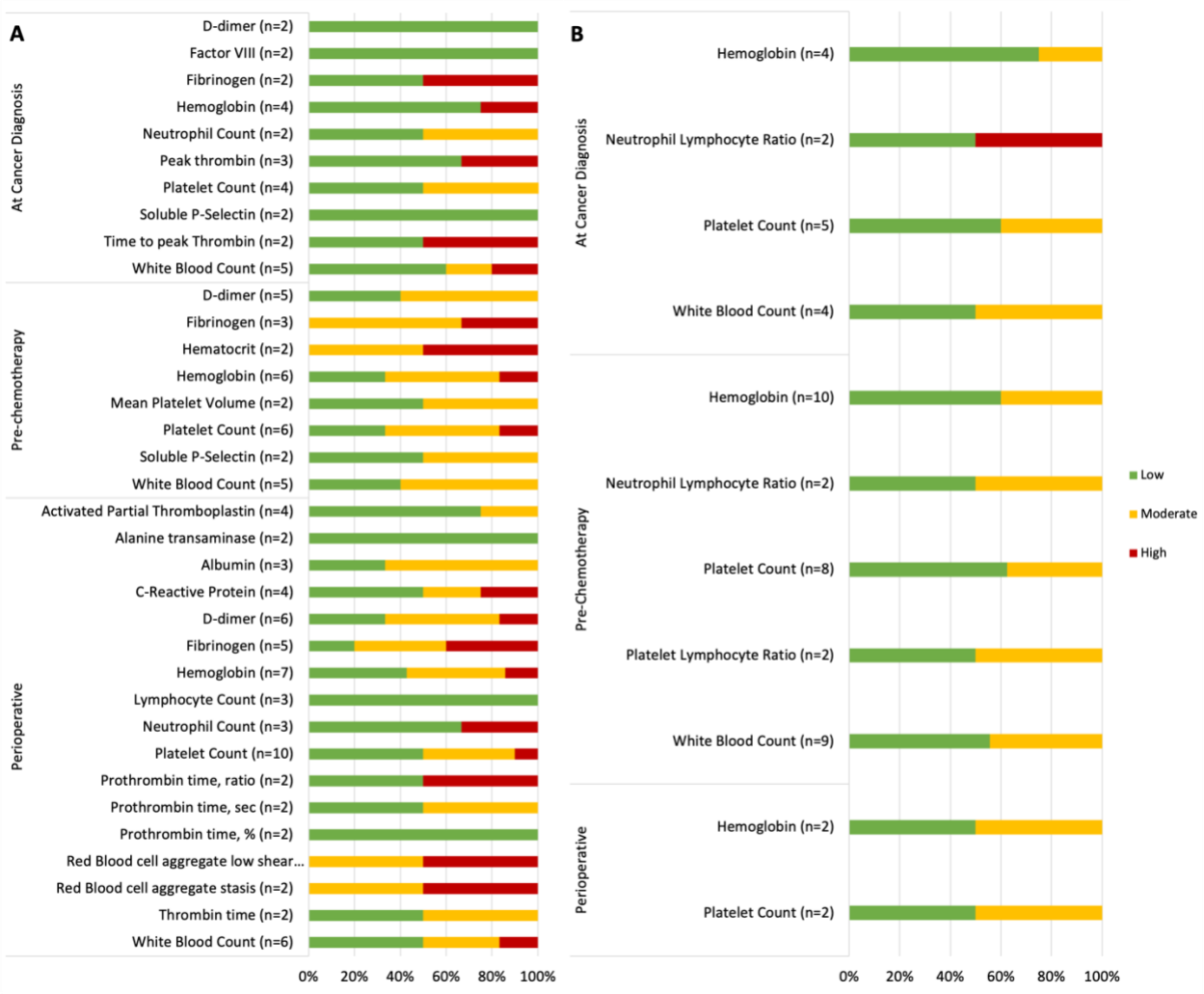
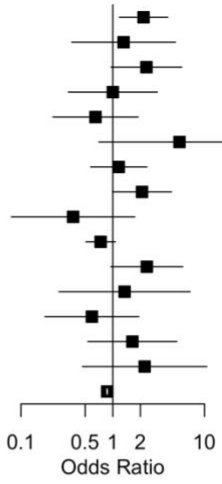


Figure 2. Overall risk of bias of studies included in the a) median/mean differences and b) pooled odds ratio meta-analyses of each biomarker

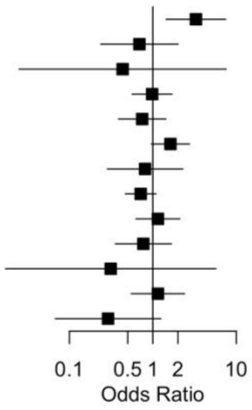
A) Hemoglobin < 100 g/L

Study	Timing of Measurement	Cancer type	OR	95%-CI
Chen 2021	At cancer diagnosis	Colorectal	2.17	[1.18; 3.97]
Wang 2018	At cancer diagnosis	Liver	1.31	[0.36; 4.82]
Li 2015	At cancer diagnosis	Pancreas	2.33	[0.96; 5.65]
Munoz-Martin 2018	At cancer diagnosis	Various	1.00	[0.33; 3.06]
Yu 2015	Pre-chemotherapy	Colorectal	0.65	[0.22; 1.89]
Rupa-Matysek 2018 (2)	Pre-chemotherapy	Lung	5.33	[0.70; 40.35]
Kuderer 2018	Pre-chemotherapy	Lung	1.16	[0.57; 2.35]
Rupa-Matysek 2018	Pre-chemotherapy	Lymphoma	2.08	[0.99; 4.37]
Bagratuni 2013	Pre-chemotherapy	Myeloma	0.37	[0.08; 1.74]
Sanfilippo 2021	Pre-chemotherapy	Myeloma	0.74	[0.51; 1.07]
Boone 2019	Pre-chemotherapy	Pancreas	2.35	[0.95; 5.80]
Kitayama 2017	Pre-chemotherapy	Various	1.35	[0.26; 6.97]
Khorana 2022	Pre-chemotherapy	Various	0.59	[0.18; 1.92]
Ferroni 2015	Pre-chemotherapy	Various	1.63	[0.54; 4.99]
Lee 2016	Preoperative	Colorectal	2.23	[0.47; 10.60]
Boone 2019	Preoperative	Pancreas	0.87	[0.86; 0.88]



B) Platelet Count ≥ 350 x 10^9/L

Study	Timing of measurement	Cancer type	OR	95%-CI
Chen 2021	At cancer diagnosis	Colorectal	3.29	[1.45; 7.47]
Lopez-Salazar 2019	At cancer diagnosis	Gynecologic	0.69	[0.24; 2.01]
Wang 2018	At cancer diagnosis	Liver	0.43	[0.02; 7.57]
Li 2015	At cancer diagnosis	Pancreas	0.98	[0.56; 1.70]
Munoz-Martin 2018	At cancer diagnosis	Various	0.75	[0.39; 1.43]
Yu 2015	Pre-chemotherapy	Colorectal	1.63	[0.96; 2.75]
Rupa-Matysek 2018 (2)	Pre-chemotherapy	Lung	0.81	[0.28; 2.29]
Kuderer 2018	Pre-chemotherapy	Lung	0.71	[0.47; 1.09]
Rupa-Matysek 2018	Pre-chemotherapy	Lymphoma	1.15	[0.63; 2.11]
Sanfilippo 2021	Pre-chemotherapy	Myeloma	0.77	[0.35; 1.67]
Kitayama 2017	Pre-chemotherapy	Various	0.31	[0.02; 5.71]
Khorana 2022	Pre-chemotherapy	Various	1.15	[0.55; 2.40]
Ferroni 2015	Pre-chemotherapy	Various	0.29	[0.07; 1.25]



C) White Blood Count > 11 x 10^9/L

Study	Timing of Measurement	Cancer type	OR	95%-CI
Chen 2021	At cancer diagnosis	Colorectal	1.70	[0.72; 4.04]
Lopez-Salazar 2019	At cancer diagnosis	Gynecologic	2.30	[0.71; 7.47]
Wang 2018	At cancer diagnosis	Liver	4.28	[1.08; 16.90]
Munoz-Martin 2018	At cancer diagnosis	Various	1.21	[0.64; 2.29]
Yu 2015	Pre-chemotherapy	Colorectal	2.33	[1.14; 4.79]
Rupa-Matysek 2018 (2)	Pre-chemotherapy	Lung	0.86	[0.26; 2.85]
Kuderer 2018	Pre-chemotherapy	Lung	0.86	[0.54; 1.34]
Sanfilippo 2021	Pre-chemotherapy	Myeloma	0.98	[0.45; 2.12]
Boone 2019	Pre-chemotherapy	Pancreas	0.94	[0.40; 2.21]
Kitayama 2017	Pre-chemotherapy	Various	0.84	[0.04; 16.98]
Khorana 2022	Pre-chemotherapy	Various	0.83	[0.36; 1.93]
Connolly 2010	Pre-chemotherapy	Various	2.58	[1.62; 4.12]
Ferroni 2015	Pre-chemotherapy	Various	0.74	[0.25; 2.20]

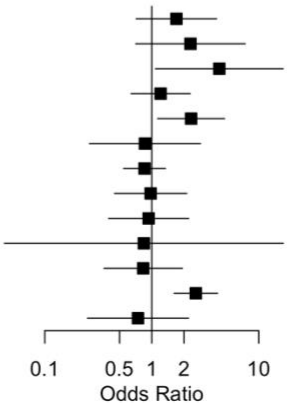


Figure 3. Forest plot of the odds ratio for the association of the Khorana score blood parameters with VTE risk

4.7 Appendix

Supplemental Data 1. Search strategy

MEDLINE

1. Venous Thromboembolism/
2. (venous adj1 thrombo*).ti,ab,kf.
3. (vein* adj1 thrombo*).ti,ab,kf.
4. Venous Thrombosis/
5. venothrombo*.ti,ab,kf.
6. pulmonary embolism/ or pulmonary infarction/
7. (pulmonary adj1 thrombo*).ti,ab,kf.
8. (pulmonary adj1 embol*).ti,ab,kf.
9. (lung adj1 embol*).ti,ab,kf.
10. (lung adj1 thrombo*).ti,ab,kf.
11. exp biomarkers/ or blood coagulation factor inhibitors/ or blood coagulation factors/
12. (biologic* adj1 marker*).ti,ab,kf.
13. (biochemical adj1 marker*).ti,ab,kf.
14. biomarker*.ti,ab,kf.
15. (clinical adj1 marker*).ti,ab,kf.
16. (surrogate adj1 endpoint*).ti,ab,kf.
17. (surrogate adj1 end adj1 point*).ti,ab,kf.
18. (surrogate adj1 marker*).ti,ab,kf.
19. (immun* adj1 marker*).ti,ab,kf.

20. (laboratory adj1 marker*).ti,ab,kf.
21. (serum adj1 marker*).ti,ab,kf.
22. (plasma adj1 marker*).ti,ab,kf.
23. Genetic Markers/
24. (genetic adj1 marker*).ti,ab,kf.
25. (dna adj1 marker*).ti,ab,kf.
26. (chromosome adj1 marker*).ti,ab,kf.
27. Genetic Predisposition to Disease/
28. (genetic adj1 predisposition*).ti,ab,kf.
29. (genetic adj1 susceptibilit*).ti,ab,kf.
30. (genetic adj2 (risk* or factor*)).ti,ab,kf.
31. (coagulation adj1 factor*).ti,ab,kf.
32. (clotting adj1 factor*).ti,ab,kf.
33. exp Genes/
34. exp Mutation/
35. (gene or genes or allele or alleles).ti,ab,kf.
36. exp Neoplasms/
37. cancer*.mp.
38. malignan*.mp.
39. (tumor or tumour).mp.
40. (neoplasm or neoplasms).mp.
41. (predict* or prognos* or risk*).ti,ab,kf.

42. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

43. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35

44. 36 or 37 or 38 or 39 or 40

45. 41 and 42 and 43 and 44

46. 45 not (exp animals/ not humans.sh.) [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

EMBASE

1. vein thrombosis/
2. (vein$ adj1 thrombo$).ti,ab,kw.
3. venous thromboembolism/
4. (venous adj1 thrombo$).ti,ab,kw.
5. venothrombo$.ti,ab,kw.
6. lung embolism/
7. (lung adj1 embol$).ti,ab,kw.
8. (pulmonary adj1 embol$).ti,ab,kw.
9. (lung adj1 thromboembol$).ti,ab,kw.
10. (pulmonary adj1 thromboembol$).ti,ab,kw.
11. deep vein thrombosis/
12. biological marker/

13. biomarker$.ti,ab,kw.
14. (biologic$ adj1 marker$).ti,ab,kw.
15. (biochemical adj1 marker$).ti,ab,kw.
16. (clinical adj1 marker$).ti,ab,kw.
17. (surrogate adj1 endpoint$).ti,ab,kw.
18. (surrogate adj1 end adj1 point$).ti,ab,kw.
19. (surrogate adj1 marker$).ti,ab,kw.
20. (immun$ adj1 marker$).ti,ab,kw.
21. (laboratory adj1 marker$).ti,ab,kw.
22. (serum adj1 marker$).ti,ab,kw.
23. (plasma adj1 marker$).ti,ab,kw.
24. genetic marker/
25. (genetic adj1 marker$).ti,ab,kw.
26. (dna adj1 marker$).ti,ab,kw.
27. (chromosome adj1 marker$).ti,ab,kw.
28. genetic predisposition/
29. (genetic adj1 predisposition$).ti,ab,kw.
30. (genetic adj1 susceptibilit$).ti,ab,kw.
31. (genetic adj2 (risk$ or factor$)).ti,ab,kw.
32. blood clotting factor/
33. (coagulat$ adj1 factor$).ti,ab,kw.
34. (clotting adj1 factor$).ti,ab,kw.

35. exp gene mutation/ or exp marker gene/ or exp gene/

36. (gene or genes or allele or alleles).ti,ab,kw.

37. exp malignant neoplasm/

38. cancer$.mp.

39. malignan*.mp.

40. (tumor or tumour).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

41. (neoplasm or neoplasms).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

42. (predict* or prognos* or risk*).ti,ab,kw.

43. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

44. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36

45. 37 or 38 or 39 or 40 or 41

46. 42 and 43 and 44 and 45

COCHRANE CENTRAL

#1 MeSH descriptor: [Venous Thromboembolism] explode all trees

#2 (venous near/1 thrombo*):ti,ab,kw

#3 (vein* near/1 thrombo*):ti,ab,kw

#4 MeSH descriptor: [Venous Thrombosis] explode all trees

#5 venothrombo*:ti,ab,kw

#6 MeSH descriptor: [Pulmonary Embolism] explode all trees

#7 (pulmonary near/1 thrombo*):ti,ab,kw

#8 (pulmonary near/1 embol*):ti,ab,kw

#9 (lung near/1 embol*):ti,ab,kw

#10 (lung near/1 thrombo*):ti,ab,kw

#11 MeSH descriptor: [Biomarkers] explode all trees

#12 (biologic near/1 marker*):ti,ab,kw

#13 (biochemical near/1 marker*):ti,ab,kw

#14 biomarker*:ti,ab,kw

#15 (clinical near/1 marker*):ti,ab,kw

#16 (surrogate near/1 endpoint*):ti,ab,kw

#17 (surrogate near/1 end near/1 point*):ti,ab,kw

#18 (surrogate near/1 marker*):ti,ab,kw

#19 (immun* near/1 marker*):ti,ab,kw

#20 (laboratory near/1 marker*):ti,ab,kw

#21 (serum near/1 marker*):ti,ab,kw

#22 (plasma near/1 marker*):ti,ab,kw

#23 MeSH descriptor: [Genetic Markers] explode all trees

#24 (genetic near/1 marker*):ti,ab,kw

#25 (dna near/1 marker*):ti,ab,kw

#26 (chromosome near/1 marker*):ti,ab,kw

#27 MeSH descriptor: [Genetic Predisposition to Disease] explode all trees

#28 (genetic near/1 predisposition):ti,ab,kw

#29 (genetic near/1 susceptibilit*):ti,ab,kw

#30 (genetic near/2 (risk* or factor*)):ti,ab,kw

#31 (coagulation near/1 factor*):ti,ab,kw

#32 (clotting near/1 factor*):ti,ab,kw

#33 MeSH descriptor: [Genes] explode all trees

#34 MeSH descriptor: [Mutation] explode all trees

#35 (gene or genes or allele or alleles):ti,ab,kw

#36 MeSH descriptor: [Neoplasms] explode all trees

#37 cancer*

#38 malignan*

#39 (tumor or tumour)

#40 (neoplasm or neoplasms)

#41 (predict* or prognos* or risk*):ti,ab,kw

#42 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)

#43 (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35)

#44 (#36 or #37 or #38 or #39 or #40)

#45 (#41 and #42 and #43 and #44)

#46 (#45 not (animal or plants or nonhuman or animal tissue or animal experiment or animal model or fungus))

Supplemental Table 1. Study characteristics of included studies

ID – First author	Year	Country	Design	N	Cancer Type	Use of Anticoa-gulation or Antiplatelet		Biomarkers
						AntiC	AntiP	
SURGERY BASED ARTICLES								
11 - Dranichnikov	2021	Sweden	PC	380	Many	Yes	-	D-Dimer, erythrocyte
46 - Rink	2020	Germany	PC	189	Genito-urinary	Yes	-	Activated partial thromboplastin time, C-Reactive Protein, Fibrinogen, Internalized Normalized Ratio, Thrombin Time, Thrombocyte
49 – Norris	2020	Ireland	PC	616	Gyne	Yes	-	Hemoglobin, Lymphocyte Count, Neutrophil Count, Platelet Count, White Blood Count
50 – Oto	2020	Italy	PC	50	Brain	Yes	Yes	Activated partial thromboplastin time, C-Reactive Protein, calprotectin, D-dimer, estimated Glomerular Filtration Rate, Fibrinogen, hemoglobin, miR's, myeloperoxidase, neutrophil count, nucleosomes, plasma cell free DNA, Platelet Count, Prothrombin Time, White Blood Count
80 – Li	2020	China	RC	3310	Breast	No	No	D-dimer, homocysteine
144 - Liang	2020	China	RC	134	Gyne	-	-	Activated partial thromboplastin time, D-dimer, Fibrinogen, Plasmin inhibitor-plasmin complex, Prothrombin time, Thrombin time, thrombin-antithrombin complex, thrombomodulin, tissue plasminogen activator-plasminogen activator inhibitor-1 complex

149 – Zhou	2020	China	RC	233	Ovarian	Yes	-	Activated partial thromboplastin time, albumin, D-dimer, Fibrinogen, Platelet Count, Prothrombin Time, Thrombin time
289 – Cui	2018	China	PC	234	Breast	-	-	D-dimer, Hemoglobin, Mean Platelet Volume, Platelet Count, Platelet Distribution Width, White Blood Count
290 - Matsuo	2018	Japan & USA	RC	906	Uterine	-	-	CA-125
368 - Wang	2019	China	PC	323	Lung	-	-	D-dimer
399 - Unruh	2017	China	PC	29	Brain	-	-	tissue factor microparticles activity
446 - Saadeh	2016	Ireland	PC	96	Gyne	Yes	-	Endogenous thrombin potential, lag-time, Prothrombin time, Time To Peak
653 - Wu	2013	China	RC	183	Ovarian	Yes	-	CA-125, D-dimer, hemoglobin, Platelet Count, Prothrombin time, White Blood Count
702 - Rojnuckarin	2012	Thailand	Nested CC	308	Many	No	-	Eosinophil count, hemoglobin, Lymphocyte Count, Mean Corpuscular Volume, Monocyte Count, Neutrophil Count, Platelet Count, White Blood Count
787 - Kusunoki	2011	Japan & USA	PC	60	Gastric	-	-	D-dimer
896 - Stender	2009	Denmark	PC	176	Colorectal	No	-	D-dimer
1108 - Iversen	2002	Denmark	PC	137	Colorectal	Yes	-	Prothrombin fragment 1+2, soluble fibrin, Thrombin-antithrombin complex

1158 – Sonaglia	1999	Italy	Post-hoc RCT	157	CNS	Yes	-	Soluble fibring polymers
S002 - Albertin	2015	USA	RC	107	Gyne	-	-	CA-125, Platelet Count
S008 – Von Tempelhoff	1998	Germany	PC	46	Ovarian	--	--	Fibrinogen, Hematocrit, Hemoglobin, Plasma viscosity, Platelet Count, Red Blood Cell aggregate low shear, Red Blood Cell aggregate stasis, White Blood Count
S017 - Khan	2019	USA	CC	447	Many	Yes	-	Albumin
S020 - Kodama	2009	Japan	PC	75	Gyne	Yes	-	Activated Partial Thromboplastin Time, C-Reactive Protein, d-dimer, hemoglobin, Platelet Count, Prothrombin Time
S022 - Lee	2016	Korea	PC	400	Colorectal	No	-	D-dimer, hemoglobin, Platelet Count, White Blood Count
S039 - Yang	2012	China	RC	1001	Lung	No	-	D-dimer
S048 - Von Tempelhoff	1995	Germany	PC	43	Breast	--	--	Fibrinogen, Plasma viscosity, Red blood cell aggregation stasis
S049 – Von Tempelhoff	1997	Germany	PC	58	Ovarian	Yes	-	Antithrombin, CA-15, D-dimer, Fibrinogen, plasminogen activator inhibitor activity, Protein C, CA-153, CA-724, CEA
S050 – Von Tempelhoff	2000	Germany	PC	261	Gyne or Breast	No	-	Plasma viscosity, Red Blood Count aggregate low shear and stasis
4943 - Huang	2022	Canada	PC	131	Brain	No	-	D-dimer, Platelet Count

5515 - Kaida	2021	Japan	PC	126	Gastric	Yes	Yes	Activated partial thromboplastic Time, Alanine Transaminase, Albumin, Aspartate Aminotransferase, C-reactive protein, Creatinine, D-dimer, hemoglobin, Lymphocyte Count, Neutrophil Count, Platelet Count, Prothrombin time, Total Bilirubin, White Blood Count
S037 – Tham	2017	USA	RC	306	Head and Neck	Yes	Yes	Lymphocyte Count, Platelet Count, Platelet Lymphocyte Ratio, White Blood Count
A1 - Wang	2014	USA	RC	2076	Bladder	Yes	--	Rhesus antibody
S051 - Boone	2019	USA	RC	426	Pancreas	Yes	--	CA 19-9. Hemoglobin, Lymphocyte count, Neutrophil Lymphocyte Ratio, Platelet Lymphocyte Ratio
S054 - Shi	2021	China	RC	492	Brain	No	--	Activated partial thromboplastin time, alanine transaminase, creatinine, D-dimer, Fibrinogen, International normalized ratio, low-density lipoprotein, Platelet Count, Prothrombin time, thrombin time, total cholesterol, triglycerides, uric acid, White Blood Count
S055 - Merkow	2011	Many	PC	44656	Many	--	--	Albumin, Platelet Count
S057 - Sinnamon	2018	USA	PC	255	Colorectal	Yes	--	Albumin, Hemoglobin, Platelet Count, White Blood Count
ANY TREATMENT BASED ARTICLES								
13 - Rupa-Matysek	2018	Poland	RC	428	Lymphoma	--	Yes	Hemoglobin, Neutrophil Count, Platelet Count, White Blood Count
43 – Nazari	2019	Austria	PC	76	Brain	Yes	--	Tumor necrosis factor alpha, Vascular endothelial growth factor

109 – Posch	2020	Austria	PC	167	Many	Yes	--	Platelet Count, White Blood Count
118 – Lopez-Salazar	2019	Mexico	RC	119	Gyne	--	--	Lymphocyte Count, Monocyte Count, Neutrophil Count, Platelet Count, White Blood Count
139 – Schorling	2020	Germany	PC	100	Many	Yes	--	D-dimer, Endogenous thrombin potential in PPP, Endogenous thrombin potential in PRP, Hemoglobin, Immature platelet function, lagtime in PPP, lagtime in PRP, Platelet Count, sP-selectin, time to peak thrombin in PPP, time to peak thrombin in PRP, White Blood Count
157 – Posch	2019	Austria, Russia	PC	815	Many	--	Yes	50% Lysis, Amplitude, Baseline Optical Density, Clot Lysis Time, Lagphase, Maximum Clot Formation Rate, Maximum Clot Lysis rate, Peak Absorbance, Time to Maximum Clot Formation, Time to peak absorbance
163 – Oto	2020	Denmark	Nested CC	32	GastroI	--	--	Calprotectin, Myeloperoxidase, Neutrophil Count, Nucleosomes, plasma cell free DNA, White Blood Count
241 – Pabinger	2018	Austrua	PC	1423	Many	--	--	D-dimer, Factor VIII, Fibrinogen, Hemoglobin, Mean Platelet Volume, Neutrophil Count, Peak thrombin, Platelet Count, Soluble P-selectin, Velocity Index of Thrombin Generation, White Blood Count
246 – Gezelius	2018	Sweden	RC	123 or 115	Lung	Yes - SA	--	Extracellular Vesicle Tissue Factor, Procoagulant Phospholipids, Endogenous thrombin potential, Peak thrombin, time to peak thrombin, total tissue factor
247 – Fotiou	2018	Greece	PC	144	MM	Yes	Yes	Antithrombin, D-dimer, Endogenous thrombin potential, Factor V, Factor VII activity, fibrin monomer, heparinase, lag-time, mean rate

								index of thrombin generation, P-selectin, peak concentration of thrombin, Procoagulant phospholipid dependent clotting time, thrombomodulin activity, time to reach the peak concentration of thrombin, tissue-factor activity, tissue factor pathway inhibitor
256 – Syrigos	2018	Greece	PC	150	Lung	No	--	activated factor VII, antithrombin, D-dimer, endogenous thrombin potential, factor V, fibrin monomer, heparinase, lag-time, mean rate index of thrombin generation, P-selectin, peak thrombin, procoagulant phospholipid dependent clotting time, time to peak thrombin, tissue factor activity
274 – Munoz-Martin	2018	Spain	PC	391	Many	No	--	Hemoglobin, Platelet Count, White Blood Count
287 – Mauracher	2018	Austria	PC	946	Many	--	--	Cell-free DNA, Citrullinated histone H3, nucleosomes
325 – Guadagni	2017	Italy	RC	342	Many	No	No	fasting blood glucose, fasting insulin, Hemoglobin A1C. HOMA index
336 – Kitayama	2017	Japan	PC	97	Many	--	--	D-dimer, Hemoglobin, plasmin alpha2-plasmin inhibitor complex, Platelet Count, Thrombin-antithrombin III complex, White Blood Count
360 – Riedl	2017	Austria	PC	62	Many	--	--	Activated Glycoprotein IIb/IIIa, Activated Glycoprotein IIb/IIIa activated by glycoprotein VI, Activated Glycoprotein IIb/IIIa activated by Protease-activated-1, Activated Glycoprotein IIb/IIIa activated by Protease-activated-4, Monocyte-platelet aggregates, Monocyte-platelet

								aggregates activated by glycoprotein VI, Monocyte-platelet aggregates activated by Protease-activated-1, Monocyte-platelet aggregates activated by Protease-activated-4, P-selectin, P-selectin activated by glycoprotein VI, P-selectin activated by Protease-activated-1, P-selectin activated by Protease-activated-4
385 – Faille	2018	France	PC	41	Pancreas	--	--	CA 19-9, D-dimer, Extracellular DNA, Factor VIII, Fibrinogen, Free tissue factor pathway inhibitor, hemoglobin, Interleukin-6, Microvesicle-tissue factor activity, Platelet Count, Soluble P-selectin, Thrombin-peak, thrombin-antithrombin complex, Von Willebrand factor, White Blood Count
397 – Park	2017	South Korea	PC	241	Gastric	--	--	C-reactive protein, CA 19-9, CA 72-4, CEA, D-dimer, Fibrinogen, hemoglobin, Plasminogen activator inhibitor-1, Platelet Count, White Blood Count
452 – Konigsbrugge	2016	Austria	PC	1070	Many	Yes	Yes	Albumin, Cholinesterase, Estimated Glomerular filtration rate, White Blood Count
460 - Pépin	2015	Netherlands, Italy, France, Mexico	nested CC	160	Many	--	--	D-dimer, Hemoglobin, Platelet Count, Prothrombin F1+2, Soluble P-Selectin, Von Willebrand factor, White Blood Count
469 – Posch	2016	Austria	PC	804	Many	No	--	Vascular Endothelial growth factor A

475 – Tafur	2016	USA	PC	241	Solid	No	--	Factor VIII, Protein C
477 – Jianlong	2015	China	C	1473	Brain	--	--	Antithrombin, D-dimer, Factor VII, Factor VIII, protein C, protein S, Von Willebrand factor antigen
493 – Matsuo	2015	USA	CC	1308	Gyne	--	--	CA-125, interleukin-6, Platelet Count
526 – Ay	2014	Austria	PC	1361	Many	Yes	Yes	D-dimer
532 – Kovacs	2015	Canada, USA	Post hoc RCT	153	MM	--	--	D-dimer, Factor VIII, thrombin-antithrombin III complex
552 – Ferroni	2014	Italy	RC	539	Many	--	--	Mean Platelet Volume
563 – Thaler	2014	Austria	PC	141	Brain	Yes	Yes	C-reactive protein, Hemoglobin, Platelet Count, White Blood Count
589 – Reitter	2014	Austria	PC	726	Many	Yes	--	Chemokine Ligand 3, Interleukin-10, Interleukin-11, Interleukin-1b, Interleukin-3, Interleukin-4, Interleukin-6, Interleukin-8
622 - Bharthuar	2013	USA	RC	103	Pancreaticobiliary	--	--	Microparticle associated tissue factor
631 – Bagratuni	2013	Greece	RC	200	Myeloma	Yes	Yes	Estimated Glomerular filtration rate, Hemoglobin, Lactate Dehydrogenase, Platelet Count
636 – Dickmann	2013	Austria	PC	832	Many	--	--	Platelet Count, White Blood Count
708 – Ahlbrecht	2012	Austria	RC	747	Many	--	--	D-dimer
736 – Ferroni	2012	Italy	RC	208	Many	No	--	Protac-induced coagulation inhibitor percentage

786 – Almasi	2011	Czech	RC	111	MM	Yes	--	beta2-microglobulin, C-reactive protein, Calcium, Creatinine, Hemoglobin, Immunoglobulin at urea, Lactate dehydrogenase, Monoclonal immunoglobulin at serum, Platelet Count
803 – Hoke	2011	Austria	PC	23	Brain	--	--	D-dimer
815 – Kanz	2011	Austria	PC	705	MM	--	--	C-Reactive Protein
832 – Poruk	2010	USA	RC	133	Pancreas	--	--	Platelet Count, Platelet Factor 4
858 – Simanek	2010	Austria	PC	665 or 514	Many	Yes	Yes	Platelet Count, thrombopoietin, White Blood Count
862 – Mandala	2009	Italy	PC	381	Many	--	--	Hemoglobin, homocysteine, Platelet Count, Protein C, Protein S, White Blood Count
882 - Vormittag	2009	Austria	PC	840	Many	Yes	Yes	Factor VIII activity
892 - Ay	2009	Austria	PC	821	Many	Yes	Yes	Prothrombin Fragment F1+2
1021 – Piektty	2005	France	RC	77	Germ-cell	Yes	--	Lactate Dehydrogenase
1029 – Streetly	2005	USA	PC	15	MM	No	--	D-dimer
2064 – Tabernero	2018	Multi	Post hoc RCT	447 or 437	Colorectal	--	--	Vascular Endothelial Growth Factor-D

2073 – Grilz	2018	Austria	PC	1469	Many	Yes	Yes	Neutrophil Lymphocyte Ratio
3437 – Ferroni	2012	Italy	PC	108	Lung	No	--	D-dimer
3872 – Cini	2010	Italy	PC	266	MM	--	--	Acquired Activated Protein C Resistance, Factor VIII, Lupus anticoagulant
4708 – Gardini	2016	Italy	RC	132	Colorectal	--	--	High-sensitivity C-reactive protein
4770 - Chalayer	2022	France, Belgium, Switzerland	RC	647	MM	Yes	Yes	gamma globulin level
4823 - Roy	2022	Canada	Post hoc RCT	476	Many	Yes	Yes	Growth Differentiation Factor 15, high-sensitivity Troponin T, N-terminal pro-B-type natriuretic peptide
4964 - Li	2021	China	PC	602	Lung	No	--	Carcinoembryonic antigen, D-dimer, Hemoglobin, Neutrophil Count, Platelet Count
5059 – Khorana	2022	USA	Nested CC	124	Many	Yes	--	Carbonic anhydrase 9, Folate Receptor, Granulocyte colony-stimulating factor, Growth Hormone, Hemoglobin, Heparin-binding EGF-like growth factor, human hcorionic gonadotropin Beta, human epidermal growth factor receptor 2, interferon-inducible T-cell alpha chemoattractant, interleukin-1 receptor type 1, interleukin-16, leukocytes, mast/stem-cell growth factor receptor, MHC class I chain-

								related protein A, Monocyte chemotactic protein 4, myoglobin, p-selectin, placenta growth factor, platelet Count, pulmonary and activation regulated chemokine, stromal cell derived factor 1, superoxide dismutase 1 soluble, thyroid stimulating hormone
5083 – Conteduca	2022	Italy	PC	180	Prostate	No	--	Albumin, alkaline phosphatase, Hemoglobin, Lactate Dehydrogenase, Neutrophil Lymphocyte Ratio, plasma tumor DNA fraction, serum chromogranin
704 – Roselli	2012	Italy	PC	217	Gastroi ntestina l	No	No	D-dimer
S003 – Arpaia	2009	Italy	PC	124	Many	No	No	D-dimer
S005 – Ay	2010	Austria	PC	1033	Many	--	--	area under thrombin generation curve, lag phase, Peak thrombin, time to peak thrombin, velocity index of thrombin generation
S006 - Ay	2008	Austria	PC	687	Many	--	Yes	Soluble P-selectin
S008 – Von Tempelhoff	1998	Germany	PC	46	Ovarian	--	--	Fibrinogen, Hematocrit, Hemoglobin, Plasma viscosity, Platelet Count, Red Blood Cell aggregate low shear, Red Blood Cell aggregate stasis, White Blood Count
S009 – Connolly	2010	USA	PC	4405	Many	--	--	Hemoglobin, Platelet Count, White Blood Count
S014 – Ferroni	2015	Italy	PC	380	Many	No	--	Hemoglobin, Neutrophil Lymphocyte Ratio, Platelet Count, Platelet Lymphocyte Ratio, White Blood Count

S015 – Fuentes	2018	USA	RC	112	Gastric	No	--	Hemoglobin, Lymphocyte Count, Neutrophil Lymphocyte Ratio, Neutrophils, Platelet Count, Platelet Lymphocyte Ratio
S016 – Rupa-Matysek	2018	Poland	RC	118	Lung	Yes	Yes	Hemoglobin, Platelet Count, White Blood Count
S019 - Kirwan	2015	UK	PC	134	Breast	No	--	D-dimer, E-selectin, Fibrinogen, vascular cell adhesion molecule I
S021 – Kruger	2017	Germany	RC	109	Pancreas	--	--	Activated partial thromboplastin time
S023 – Li	2015	USA	RC	670	Pancreas	Yes	Yes	Blood glucose, CA 19-9, Complete Blood Count, Hemoglobin, Platelet Count
S026 – Mansfield	2016	USA	PC	719	Lung	No	Yes	Hemoglobin, Platelet Count, White Blood Count
S031 – Posch	2016	Austria	PC	1685	Many	--	--	D-dimer, Hemoglobin, Platelet Count, White Blood Count
S036 – Thaler	2012	Austria	PC	60 or 72 or 119 or 148 or 43	Pancreas, Brain, Stomach or Colorectal	--	--	Microparticle associated tissue factor activity

				or 126				
S038 – Wang	2018	USA	RC	270	Liver	--	--	Hemoglobin, Platelet Count, White Blood Count
S042 – Zwicker	2012	USA	RCT	66	Many	No	No	Tissue factor bearing microparticles
S043 – Kuderer	2018	N & S America, Europe, Asia	PC	1980	Lung	--	--	Hemoglobin, Platelet Count, White Blood Count
S046 – Van Es	2017	Netherlands, Italy, France, Mexico	PC	876	Many	No	Yes	Hemoglobin, Platelet Count, White Blood Count
S048 - Von Tempelhoff	1995	Germany	PC	43	Breast	--	--	Fibrinogen, Plasma viscosity, Red blood cell aggregation stasis
4961 - Otasevic	2022	Serbia	PC	706	Lymphoma	Yes	--	Albumin, C-reactive protein, erythrocyte sedimentation rate, Fibrinogen, Hemoglobin, Lactate dehydrogenase, Leukocytes, Neutrophil Lymphocyte Ratio, Platelet Lymphocyte Ratio, Platelet Count, Total proteins
364 – Moeini	2017	USA	RC	714	Gyne	Yes	--	CA-125, Platelet Count

S051 - Boone	2019	USA	RC	426	Pancreas	Yes	--	Hemoglobin, Lymphocyte count, Neutrophil count, Neutrophil Lymphocyte Ratio, Platelet Count, Platelet Lymphocyte Ratio, White Blood Count
S052 - Chen	2021	China	RC	245	Colorectal	--	--	Carcinoembryonic antigen, D-dimer, Hemoglobin, Platelet Count, White Blood Count
S053 - Kuk	2017	Poland	RC	57	Ovarian	Yes	--	Activated partial thromboplastin time, D-dimer, Fibrinogen, Hemoglobin, International normalized ratio, Platelet Count, Prothrombin time, White Blood Count
S056 - Yu	2015	Canada	RC	499	Colorectal	Yes	Yes	Hemoglobin, Platelet Count, White Blood Count
S058 - Sanfilippo	2021	USA	RC	2870	MM	Yes	Yes	Hemoglobin, Platelet Count, White Blood Count

Abbreviations: CC=case-control, C-cohort=case-cohort, CNS=Central Nervous System, Gyne=Gynecologic, MM=Multiple Myeloma, PC=prospective cohort, RC=retrospective cohort, RCT=randomized control trial

Supplemental Table 2. Outcome and treatments of included studies

ID – First author	Outc-ome	F/U Time[a] (months)	Definition of Outcome	Surgical Procedures and Treatments
SURGERY BASED ARTICLES				
11 - Dranichnikov	VTE	6	Hospitalizations for VTE recorded in the Swedish In-Patient Register. Diagnosis without details on positive or negative radiological examinations.	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy
46 - Rink	VTE	1	VTE defined as clinically apparent or diagnostic-confirmed DVT and/or PE.	Radical cystectomy, bilateral pelvic lymph node dissection
49 – Norris	VTE	24	Objectively confirmed VTE - by documented objective testing such as C/U, venography, or CT and CTPA in the case of PE – incidental/ asymptomatic events (ie. Routine CT) included when the event required treatment	Gynecologic cancer surgery (open or laparoscopic)
50 – Oto	PE	0.07-0.23	Preoperative V/Q scan was performed to rule out pre-existing PE. All patients underwent a second V/Q scan 2-7 days post-surgery. If the scan was PE-positive, a confirming CT was performed. Events required a positive V/Q scan and CT. C/U of the legs was performed in PE patients to check for DVT.	Removal of intracranial tumor
80 – Li	VTE	0.33-0.43	Symptomatic or occult VTE diagnosed by one of the methods: CDUS, CT, angiography, or MRI. Occult VTE defined as VTE detected by imaging performed for other reasons than VTE	Lumpectomy, Mastectomy, Modified typical radical mastectomy, combined

			suspicion (ie. assessment of response to treatment, complications or cancer re-staging). Events obtained through medical record review.	implant reconstruction, mastectomy and autologous tissue breast reconstruction,
144 - Liang	VTE	Unclear	Diagnosis made by intravenous ultrasound by radiologist.	Hospitalization admission
149 – Zhou	VTE	1	Diagnosis based on clinical signs and DVT confirmed by CDUS; PE diagnosed by spiral CT.	Cytoreduction surgery
289 – Cui	DVT	12	C/U performed prior to surgery, 1-, 3-, 6-, and 12-months post-surgery. If patients showed clinical signs of DVT, additional C/U was performed.	Complete surgical resection of breast cancer
290 - Matsuo	VTE	32.2-36.5	Only collected symptom-based VTE. VTE diagnosed based on radiographic imaging including CT, CTPA, V/Q scan, or DUS.	Hysterectomy
368 - Wang	VTE	Unclear	DUS was performed on all patients pre- and post-surgery to assess for DVT. If patient had PE symptoms (chest pain, hemoptysis or unexplained hypoxemia and dyspnea) or Caprini ≥ 9 or new DVT post-surgery, then CTPA was performed to determine if there is PE.	Open thoracotomy or video-assisted thoracoscopic surgery
399 - Unruh	VTE	3.9	Unspecified	Subtotal resection, gross total resection or biopsy
446 - Saadeh	VTE	12	Symptomatic VTE post-surgery was objectively confirmed by CTPA or venous DUS.	Surgery for removal of gynecological tumor
653 - Wu	VTE	Unclear	DVT diagnosed by type B ultrasonic examination and PE diagnosed by chest radiograph.	Ovarian tumor surgery
702 - Rojnuckarin	VTE	discharge + 1.5	If patients had symptoms of VTE before or on admission, they were excluded. After admission, they were monitored for VTE	Hospitalization admission

			symptoms. All patients were contacted by phone or interviewed for VTE symptoms and if there were VTE suspicions, patients were asked to come in for investigation. Symptomatic DVT diagnosed by DUS and PE diagnosed by CTA or V/Q scan.	
787 - Kusunoki	DVT	0.033	U/S performed pre-surgery and 24-hours after surgery in all patients. DVT diagnosed by U/S (computed sonography or color flow Doppler scan).	Endoscopic submucosal dissection
896 - Stender	DVT	12	C/U was performed pre-surgery, 1-week, 1-month and 1-year after surgery. At 3-, 6- and 9-months, the patients were clinically examined for signs of DVT and if there was clinical signs of DVT, additional C/U was performed to confirm diagnosis. Radiological records of neighboring hospitals were reviewed to identify DVT's diagnosed by general practitioner.	Intended curative surgery
1108 - Iversen	VTE	Unclear	Bilateral phlebography was performed 7-12 days after surgery to look for DVT.	Curative surgery in form of laparotomy
1158 – Sonaglia	DVT	Unclear	Venography performed 7-9 days after surgery and criterion for DVT diagnosis was constant intra-liminal filling defect in two+ views or after second injection of contrast.	Neurosurgery for brain or spinal tumor
S002 - Albertin	PE	1	PE based on positive postoperative CTPA in health records.	Surgery for malignant disease in inpatient operating rooms (laparoscopy and laparotomy)

S008 - Von Tempelhoff	DVT	0-38 (range)	Patients were screened for DVT presurgery, 1-, 3-, 5-, 7-, and 10-days after surgery, before each chemotherapy cycle and every three months using IPG. If result of IPG, physical examination or patients history was indicative of DVT, an ascending venography of both legs was performed. In patients with clinical symptoms of PE, V/Q scan was performed.	Chemotherapy, surgery
S017 - Khan	VTE	2	VTE discovered due to symptoms (DVT, PE or portal-splenic-mesenteric vein thrombosis) or incidental VTE found on imaging (not specified).	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy
S020 - Kodama	VTE	1	After operation, clinical signs (leg swelling, tenderness along distribution of deep veins, acute cardiovascular dysfunction, dypsnea, chest pain, and loss of consciousness) and elevation of plasma d-dimer levels (10-15ug/mL, especially > 15ug/mL) were monitored. Patients with d-dimer elevation or who showed clinical signs were subject to CT.	hysterectomy and/or para-lymphadenectomy
S022 - Lee	VTE	1	Cohort A: All patients were screened 5-14 days after surgery with duplex and color DUS. Cohort B: VTE-related symptoms and signs were checked during follow-ups assessments. Both cohorts had follow-up assessments at 4 weeks post-surgery. DUS or CTA were performed when there were symptoms or signs of VTE.	Major open or laparoscopic abdominal surgery
S037 – Tham	VTE	0.66 (mean)	VTE defined as any DVT or PE confirmed by diagnostic imaging, with either DUS for DVT, or with spiral CT for PE. Only VTEs in	Surgery

			the immediate postoperative period (during inpatient stay) were included.	
S039 - Yang	VTE	25.73	VTE diagnosis was confirmed with spiral CTPA, and CDUS.	Complete or incomplete resection of lung cancer
S048 – Von Tempelhoff	DVT	Unclear	IPG was performed at time of diagnosis and before each of the six courses of chemotherapy to assess for DVT and verified by contrast phlebography.	Chemotherapy, surgery
S049 – Von Tempelhoff	DVT	26.5	All patients were evaluated for VTE by IPG before surgery, 1-, 3-, 5-, 7-, and 10-days after surgery, before each cycle of chemotherapy and every 3-months of follow-up and in the post-operative period of second look surgery. If result of IPG, physical examination or patients history was indicative of DVT, an ascending venography was performed and a venography test was positive when there was constant intraluminal filling defect in the deep veins. In patients with clinical symptoms of PE, V/Q scan was performed.	Major cancer surgery consisting of hysterectomy, bilateral salpingo-oophorectomy, high resection of the infundibulo-pelvic ligaments, omentectomy, appendectomy, pelvic lymphadenectomy
S050 – Von Tempelhoff	VTE	43	All patients were evaluated for VTE by IPG before surgery, 1-, 3-, 5-, 7-, and 10-days after surgery, before each cycle of chemotherapy or radiation therapy, 6-9 months after surgery and every 3-6-months of follow-up. If IPG was abnormal or if patients had signs and symptoms of thrombosis, contrast phlebography or DUS was performed. A phlebography test was positive when there was constant intraluminal filling defect and duplex U/S was positive	Gyn: midline abdominal incision and included initial peritoneal lavage for cytological evaluation, hysterectomy, bilateral salpingo- oophorectomy, high resection of the infundibulo-pelvic ligaments, omentectomy, appendectomy, and pelvic lymphadenectomy. Breast:

			when there was a lack of compressibility. In patients with clinical signs of PE or confirmed diagnosis of thrombosis, V/Q scan was performed and the test was positive for PE when the scan had high probability of PE.	either modified radical mastectomy or lumpectomy (segmental mastectomy) both with dissection of level I and II axillary lymph nodes
4943 – Huang	VTE	15.8	Either deep venous thrombosis (DVT), pulmonary embolus (PE), or cerebral venous sinus thrombosis (CVST) confirmed by imaging occurring within 18 months after inclusion.	Total or subtotal tumor (glioblastoma) resection
5515 - Kaida	VTE	1	symptomatic and asymptomatic VTE during 30 days after surgery. CT or U/S the lower limb was performed postoperatively when symptoms of VTE such as respiratory distress, extremity edema, or leg pain were observed, or the postoperative blood test showed levels of SF ≥7.6 μg/ mL or D-dimer ≥9.8 μg/mL on day 1 despite no symptoms of VTE.	Radical gastric cancer surgery including: distal gastrectomy, total gastrectomy, proximal gastrectomy
A1 - Wang	VTE	133.2	Patients were evaluated for VTE was based on symptoms and/or clinical evaluation. No routine screening was involved. During the early half, the diagnosis of DVT was made by venography and during the latter half, duplex U/S was used. Similarly, the diagnosis of PE was based on arteriography or V/Q scan interpreted by a radiologist suggestive of a high probability for PE, or if a filling defect was present on contrast-enhanced CT.	Radical cystectomy with or without neoadjuvant or adjuvant chemotherapy

S051 - Boone	VTE	3	VTE defined as DVT, PE, and portal, superior mesenteric or splenic vein thrombosis. No screening was performed to identify VTE.	Surgical resection of pancreatic adenocarcinoma with or without adjuvant chemotherapy
S054 - Shi	DVT	1	Preoperative U/S conducted to exclude patients with a previous history of DVT. No screening for DVT after surgery; when patients had symptoms or an increase in D-dimer level ≥ 10 mg/L after the operation, U/S was performed to confirm symptomatic DVT.	Craniotomy
S055 - Merkow	VTE	1	VTE within 30 days of the index operation. DVT was defined as a new blood clot confirmed by duplex U/S, venogram or CT scan. PE was defined as a blood clot in the pulmonary artery confirmed by V/Q scan, CT scan or pulmonary arteriogram.	Surgery for cancer with or without chemotherapy or radiotherapy
S057 - Sinnamon	DVT	min: 1	Proximal (involving the femoral, profunda femoral, or popliteal vein) or distal (involving venous structures below the knee) DVT were included. DVT was identified by duplex U/S of the bilateral lower extremities which was routinely performed postoperatively (target: day 4 post-operative).	Abdominal surgery for malignant indication
ANY TREATMENT BASED ARTICLES				
13 - Rupa-Matysek	VTE	37	No routine screening for VTE. DUS and color imaging were used to diagnose DVT in symptomatic patients and CTA was performed to detect PE.	Chemotherapy
43 – Nazari	VTE	11.77	Objectively confirmed VTE.	Chemotherapy

109 – Posch	VTE	8.22	Composite of symptomatic and objectively confirmed DVT and/or PE. All events were adjudicated by a panel. Incidental PE counted as an event if it required anticoagulation. Fatal PE was defined as PE if it was the cause of death on autopsy record or PE was the immediate cause of death.	Chemotherapy
118 – Lopez-Salazar	VTE	Unclear	DUS and CT images were reviewed for VTE.	Surgery, Chemotherapy
139 – Schorling	VTE	3.03	Screenings for VTE were not performed. DUS and/or CT were carried out in case of clinical symptoms. Incidental, asymptomatic VTE counted as an event if it required anticoagulant treatment. VTE was defined as PE and DVT at any location including limb and abdomen.	Chemotherapy
157 – Posch	VTE	24	Objectively confirmed symptomatic VTE, defined as a composite of DVT and/or PE. Incidental VTEs were considered when they warranted therapeutic anticoagulation. Screening for VTE was not performed.	Surgery, chemotherapy. radiotherapy
163 – Oto	VTE	24	Patients were screened for DVT by bilateral C/U and PE by CTPA every three months, beginning at cancer diagnosis. Patients who underwent curatively intended surgery were examined preoperatively and postoperatively.	Surgery, chemotherapy, neodjuvant treatment, palliative gemcitabine
241 – Pabinger	VTE	5.92	Symptomatic, objectively confirmed VTE, defined as distal or proximal DVT of the leg, upper extremity DVT, symptomatic	Surgery, chemotherapy, radiotherapy

			splanchnic DVT and/or PE. Incidental PEs counted as events if they required anticoagulation. Upper extremity DVT related to indwelling venous catheters and incidental splanchnic vein thrombosis were not considered as events.	
246 – Gezelius	VTE	9.07	Unspecified.	Chemotherapy, Radiotherapy
247 – Fotiou	VTE	15.5	Symptomatic objectively confirmed VTE using either CDUS, CT, MRI or scintigraphy. Symptomatic VTE included DVT, PE or both, SVT located at distance of <3 cm from the saphenofemoral junction, CVC thrombosis or upper limb vein thrombosis or vein thrombosis of rare localization (i.e., splanchnic vein or cerebral vein thrombosis). Incidental VTE were not included.	Anti-myeloma
256 – Syrigos	VTE	12	Symptomatic and objectively confirmed VTE, including DVT, PE, or both, CVC thrombosis, upper limb vein thrombosis, or vein thrombosis at a rare localization (i.e., splanchnic vein or cerebral vein thrombosis). Symptomatic VTE had to be documented using CDUS, CT, MRI or scintigraphy. The investigators took into consideration the results of the imaging methods and the administration of doses of anticoagulation. Patients with incidental VTE were not included.	Chemotherapy
274 – Munoz-Martin	VTE	18	DVT in the lower limbs diagnosed by U/S or ascending venography. PE diagnosed by VQ scan, pulmonary angiography, or spiral CT. Intracranial venous thrombosis was diagnosed by MRI.	Chemotherapy

287 – Mauracher	VTE	24	Symptomatic or fatal, objectively confirmed VTE. CTPA of the chest or VQ scan or autopsy used to diagnose PE and C/U or venography for DVT.	Chemotherapy, Surgery, Radiotherapy
325 – Guadagni	VTE	11	Patients were regularly seen at scheduled visits; additional visits were arranged at the occurrence of clinically suspected VTE. VTE was defined as first symptomatic or asymptomatic VTE episode during active treatment. DVT was confirmed by venography or CDUS (in proximal DVT only). PE was diagnosed by spiral CT.	Pre-study surgery, chemotherapy
336 – Kitayama	VTE	3	DVT confirmed by doppler and PE confirmed by CT.	Chemotherapy
360 – Riedl	VTE	24	No routine screening for VTE. VTE confirmed by objective imaging methods such as duplex U/S or venography for DVT or by CT or VQ scan for PE.	Chemotherapy, surgery, radiotherapy
364 – Moeini	VTE	28.8	Written medical records and radiology reports including DUS, CT, pulmonary angiogram, and VQ scan were reviewed for the diagnosis of VTE.	Unclear
385 – Faille	VTE	5.56	No systematic screening for VTE. Symptomatic VTE were confirmed by either DUS, venography, or CT-scan. Incidental VTE were also considered.	Chemotherapy, surgery, radiotherapy
397 – Park	VTE	10.8	Symptomatic VTE diagnosed using DUS and/or CT venography to detect DVT, while chest CT and/or pulmonary artery CT	Chemotherapy

			angiography were employed to detect PE. Incidentally detected VTE also counted as an event.	
452 – Konigsbrugge	VTE	23.77	All VTE events, based on objective imaging evidence.	Unclear
460 - Pépin	VTE	6	VTE were diagnosed by CT scan for PE or DUS for DVT. They were performed in two circumstances: (i) when the patients had symptoms (symptomatic); and (ii) when staging the cancer (incidental/asymptomatic).	Chemotherapy, EPO treatment, Radiotherapy, Angiogenesis inhibitor
469 – Posch	VTE	24	Symptomatic nonfatal and fatal VTE, but incidentally discovered VTE were also counted as an event if deemed to be of clinically significant.	Chemotherapy, surgery, radiotherapy
475 – Tafur	VTE	10.4	VTE, including symptomatic or incidentally found DVT of lower or upper limbs, PE and visceral venous thrombosis. DVT, including visceral thrombosis, was positive if imaged on CT scan, MRI, venogram or duplex U/S. PE was defined as positive in the presence of a high probability VQ scan, CT angiogram or a positive pulmonary angiogram.	Chemotherapy
477 – Jianlong	VTE	3	Symptomatic or fatal VTE, confirmed by U/S, angiographic CT or V/Q scan.	Chemotherapy, surgery, radiotherapy
493 – Matsuo	VTE	31.3	VTE was searched in both medical records and radiology reports for DUS, CT, and lung scan.	Unclear

526 – Ay	VTE	24	Objectively confirmed symptomatic or fatal VTE (DVT, PE, and other venous sites).	Chemotherapy, Surgery, Radiotherapy
532 – Kovacs	VTE	49.2	VTE confirmed by objective testing.	thalidomide-prednisone with observation alone as maintenance therapy following initial treatment, high dose melphalan and ASCT in patients with newly diagnosed MM
552 - Ferroni	VTE	8.5	First symptomatic or asymptomatic VTE, either DVT or PE.	chemotherapy, some with concurrent radiotherapy
563 – Thaler	VTE	9.93	No routine screening for VTE. Symptomatic VTE was confirmed by DUS or venography for DVT and by CTPA for PE.	chemotherapy, surgery, radiotherapy
589 – Reitter	VTE	23.18	VTE objectively confirmed by DUS, phlebography, CT or VQ scan.	Unclear
622 - Bharthuar	VTE	6.77	VTE had to be confirmed by imaging and included symptomatic or incidentally discovered DVT, visceral vein thrombosis and PE.	Unclear
631 – Bagratuni	VTE	9	VTE confirmed by DUS for DVT and CT angiography in suspect cases of PE.	immunomodulatory agent, glucocorticoid meds, proteasome inhibitor, chemotherapy
636 – Dickmann	VTE	17.33	No routine screening for VTE. Symptomatic VTE confirmed by Duplex sonography or venography for DVT and CT or VQ scan for PE.	Chemotherapy, Surgery, Radiotherapy
708 – Ahlbrecht	VTE	24	No routine screening for VTE. Only symptomatic or fatal VTE were classified as events when confirmed by objective medical imaging	chemotherapy, radiotherapy, surgery

			methods, such as duplex U/S or CT. Incidental VTE were classified as events when deemed to be clinically significant.	
736 – Ferroni	VTE	9.2	DVT was confirmed by venography or CDUS (in proximal DVT only). PE was diagnosed by spiral CT.	chemotherapy, antiangiogenic drugs, corticosteroids, hormonal therapy
786 – Almasi	VTE	Unclear	Unspecified.	Thalidomide-based treatment, cyclophophamide+Thalimomide+dexmethasone
803 – Hoke	VTE	7.3	DVT diagnosed by C/U. PE diagnosed by spiral CT with intravenous contrast.	surgery, chemotherapy, radiotherapy
815 – Kanz	VTE	24	VTE diagnosed by U/S, CT or VQ lung scan.	
832 – Poruk	VTE	Unclear	VTE confirmed through imaging such as CT or doppler.	either surgical resection and/or at least one full course of chemotherapy and/or radiation
858 – Simanek	VTE	14.56	No routine screening for VTE. Symptomatic or fatal VTE were recorded as an event. Imaging was performed in symptomatic patients. VTE was confirmed by objective methods (ie. duplex U/S or phlebography for DVT and CT for PE.	chemotherapy, surgery, radiotherapy,
862 – Mandala	VTE	35	Patients were not screened for asymptomatic VTE; only symptomatic forms were checked. The medical charts/ radiological history of all patients was checked for U/S of the limbs, chest and abdominal CT, and VQ scan. The criterion for a VTE by C/U was	chemotherapy

			non-compressibility of a proximal vein. In patients with PE symptoms, VQ scanning was conducted. In inconclusive PE cases, a spiral CT scan was required to confirm the PE.	
882 - Vormittag	VTE	16.27	No routine screening for VTE. Symptomatic or fatal VTE were recorded as events. VTE was confirmed by objective methods in symptomatic patients including duplex U/S or phlebography for DVT and CT, VQ scan, or angiography for PE. Fatal VTE events were confirmed by autopsy. Incidental VTE were accepted as events if it was clinically significant and required continuous anticoagulation.	chemotherapy, surgery, radiotherapy, chemo+radio, chemo+surgery, surgery+radio, chemo+surgery+radio
892 - Ay	VTE	16.47	Occurrence of objectively confirmed symptomatic or fatal VTE.	Chemotherapy, Surgery, Radiotherapy
1021 – Piektty	VTE	6	Any VTE or ATE (including SVT and thrombophlebitis on CVC). Radiologic evidence including, Doppler U/S, CT scan, arteriography, or phlebography was required to ascertain the diagnosis of TE	Chemotherapy, surgery
1029 – Streetly	DVT	max 8.75	Unspecified.	thalidomide, corticosteroids, anthracycline, chemotherapy
2064 – Tabernero	VTE	21.7	VTE including DVT, PE, jugular vein thrombosis, mesenteric vein thrombosis, subclavian vein thrombosis, SVT, thrombosis in device, vena cava embolism.	Ramucirumab+Chemotherapy
2073 – Grilz	VTE	24	Objectively confirmed symptomatic or fatal DVT or PE.	Chemotherapy, surgery and radiotherapy

3437 – Ferroni	VTE	6.9	DVT confirmed by venography or duplex C/U (in proximal DVT only). PE confirmed by spiral CT.	chemotherapy, erythropoietin stimulating agents, prophylactic myeloid growth factors, corticosteroids
3872 – Cini	VTE	4	Symptomatic VTE confirmed with imaging.	all patients received four monthly courses of thal (at the initial dose of100 mg⁄d for 14 days, with subsequent increase to200 mg⁄d) combined with pulsed high-dose dexametha-sone (40 mg⁄d for 4 days every 28 days, with cyclesrepeated through d 9 to 12 and d 17 to 20 on the firstand third month of therapy) as induction therapy inpreparation for subsequent double autologous stem-celltransplantatio
4708 – Gardini	VTE	36	We considered both DVT and PE for VTE. Thrombosis caused by infusion devices was excluded.	chemotherapy, bevacizumab
4770 - Chalayer	VTE	6	PE, DVT including lower and upper limbs, distal or proximal, CVC catheter-related thrombosis.	targeted therapy and immunotherapy

4823 - Roy	VTE	6	VTE defined as objectively confirmed symptomatic, or incidentally detected events including proximal DVT of the lower and upper limbs, PE, splanchnic or cerebral vein thrombosis.	surgery, chemotherapy, radiotherapy
4964 - Li	VTE	6	No routine screening for VTE. Symptomatic or incidental VTE was confirmed using objective imaging. Venous U/S or CT angiography was performed to confirm the diagnosis of DVT and the diagnosis of PE was confirmed using a CTPA or a VQ scan. Asymptomatic and incidental VTE events were included if they were determined to be clinically significant.	chemotherapy, surgery, radiotherapy, tyrosine kinase inhibitors
5059 – Khorana	VTE	6	Objectively confirmed symptomatic or asymptomatic proximal lower limb DVT, symptomatic or incidental PE, and death from VTE.	Chemotherapy, surgery, radiotherapy
5083 – Conteduca	VTE	58	All VTE and/or PE (besides SVT cases) were classified as events. VTEs had to be clinically evident and confirmed by a diagnostic test.	Chemotherapy, surgery, radiotherapy
704 – Roselli	VTE	9.8	DVT was confirmed by venography or CDUS (in proximal DVT only). PE was established by spiral CT.	Chemotherapy (6 neoadjuvant and 81 adjuvant)
S003 – Arpaia	VTE	6	Symptomatic or asymptomatic DVT and fatal or nonfatal symptomatic PE were considered the primary outcomes. Symptomatic SVT was also recorded. In patients with clinically suspected DVT or PE, routine imaging was done to confirm the	Chemotherapy

			diagnosis. Patients were screened via CUS of the leg at enrolment, after 3 and 6 months to check for asymptomatic DVT.	
S005 – Ay	VTE	17	VTE, either symptomatic or fatal VTE, confirmed by duplex U/S, phlebography, and/or CT or autopsy.	Chemotherapy, surgery, radiotherapy
S006 - Ay	VTE	13.64	No routine screening for VTE was performed. Patients with VTE symptoms underwent imaging. DVT was confirmed via duplex U/S or venography and PE was confirmed via CT or VQ scan. The endpoint was either symptomatic or fatal VTE, confirmed by previously mentioned imaging or autopsy.	Chemotherapy, surgery, radiotherapy
S008 – Von Tempelhoff	DVT	0-38 (range)	Patients were screened for DVT presurgery, 1-, 3-, 5-, 7-, and 10-days after surgery, before each chemotherapy cycle and every three months using IPG. If result of IPG, physical examination or patients history was indicative of DVT, an ascending venography of both legs was performed. In patients with clinical symptoms of PE, V/Q scan was performed.	Chemotherapy, surgery (estimate for surgery only also provided)
S009 – Connolly	VTE	2.47	No routine screening for VTE was performed. Symptomatic VTE diagnosed by the treating physician by routine diagnostic testing. These events were recorded at new-cycle and mid-cycle visits depending on the timing of the event.	Chemotherapy
S014 – Ferroni	VTE	9.2	First symptomatic or asymptomatic VTE (DVT or PE) during active treatment.	Chemotherapy, radiotherapy

S015 – Fuentes	VTE	21.3	Symptomatic or incidental DVT of the upper and lower limbs, PE, and splanchnic vein thrombosis, diagnosed by DUS, CT, CTA, and/or VQ scans.	Chemotherapy, surgery, radiotherapy
S016 – Rupa-Matysek	VTE	14	No routine screening for VTE was performed. VTE defined as symptomatic PE and DVT appearing after the lung cancer diagnosis and confirmed by imaging tests (CTA for PE or CDUS to diagnose DVT).	Chemotherapy, surgery, radiotherapy
S019 - Kirwan	VTE	3	DVT or PE and occult DVT detected by duplex U/S. Bilateral full-leg duplex U/S for DVT was performed 1 month after starting chemotherapy in all patients and repeated if VTE symptoms developed til 3 months after start of treatment.	Chemotherapy
S021 – Kruger	VTE	Unclear	VTE retrieved retrospectively from individual medical patient records.	Chemotherapy, radiotherapy
S023 – Li	VTE	60	TE events were identified based on radiological evidence. These events included DVT, PE and others such as PVT and splenic vein thrombosis. The thrombosis locations were classified as PE, DVT in the upper and/or lower limbs, and other sites including thrombosis in arteries and visceral veins.	Chemotherapy, chemoradiation
S026 – Mansfield	VTE	15.2	Symptomatic or incidental DVT of lower or upper limbs, PE and visceral venous thrombosis. VTE diagnosis was assigned based on predefined criteria: limb or visceral VTE confirmed by venogram, angiography, CT, MRI or C/U.	Chemotherapy, surgery, radiotherapy

S031 – Posch	VTE	24	Symptomatic first non-fatal or fatal VTE confirmed by leg vein C/U, venography, VQ scan, CT or CTPA of the chest, and autopsy records. No routine screening for VTE was performed, and incidentally discovered VTEs were adjudicated as an event if deemed to be of clinically significant.	Chemotherapy, surgery, radiotherapy
S036 – Thaler	VTE	9.17-21.6	Symptoms indicative of VTE (DVT or PE), stroke, myocardial infarction, or peripheral arterial thrombosis. Accidentally detected VTE counted as an event if it was of clinically significant and requested anticoagulant treatment.	Chemotherapy, surgery, radiotherapy
S038 – Wang	VTE	15.2	VTE diagnosed based on imaging including C/U, contrast-enhanced CT, and pulmonary angiogram. There was no systematic VTE screening. PVT was not included.	Chemotherapy
S042 – Zwicker	VTE	2	Symptomatic proximal or distal lower extremity DVT, symptomatic PE or fatal PE diagnosed by autopsy, or asymptomatic proximal DVT diagnosed by screening C/U.	Chemotherapy
S043 – Kuderer	VTE	6	VTE was based on clinical suspicion of a new event during clinical follow-up. Specific investigations to detect DVT and PE were performed as indicated based on clinical symptoms or physical signs of VTE as determined by the treating physician. If the patient had both a PE and lower-extremity DVT, they were counted only once and categorized as PE. Incidental VTEs found on routine staging imaging studies were included.	Chemotherapy

S046 – Van Es	VTE	6	Objectively confirmed symptomatic or incidental PE, distal or proximal leg DVT, or non-catheter-related upper extremity DVT or symptomatic CVC related DVT. Incidental events were included. Patients did not undergo screening for VTE.	Platinum based chemotherapy, gemcitabine, erythropoeitin stimulating agents
S048 – Von Tempelhoff	DVT	Unclear	IPG was performed at time of diagnosis and before each of the six courses of chemotherapy to assess for DVT and verified by contrast phlebography.	Chemotherapy, surgery (estimate for surgery only also provided)
4943 – Huang	VTE	15.8	Either DVT, PE, or cerebral venous sinus thrombosis confirmed by imaging.	Unclear
4961 - Otasevic	VTE	25	VTE diagnosed objectively based on imaging, including C/U, contrast-enhanced thoracic CT, and MRI, as well as clinical examination and laboratory evaluation.	Chemotherapy
S051 - Boone	VTE	3	VTE defined as DVT, PE, and portal, superior mesenteric or splenic vein thrombosis. No screening was performed to identify VTE.	Surgical resection of pancreatic adenocarcinoma with or without adjuvant chemotherapy
S052 - Chen	VTE	Unclear	Objective diagnosis of VTE was required; either DVT diagnosed via C/U or PE diagnosed via CTA.	Chemotherapy, radiotherapy, interventional therapy, targeted therapy
S053 - Kuk	VTE	Unclear	VTE was diagnosed based on clinical signs (i.e., extremity pain, swelling, and bruising) with confirmation by DUS. No routine screening.	Chemotherapy, surgery
S056 - Yu	VTE	Unclear	Unspecified.	Chemotherapy, surgery

S058 - Sanfilippo	VTE	6	VTE identified using a previously validated algorithm that combined ICD-9 codes with prescription for anticoagulation or an inferior vena cava filter.	Chemotherapy

Abbreviations: CDUS=color doppler ultrasound, CT=computed tomography, CTA= computerized tomographic angiography, CTPA = computed tomography pulmonary angiogram, C/U=compression ultrasonography, DVT=deep vein thrombosis, DUS= doppler ultrasound, IPG=impedance plethysmography, MRI= magnetic resonance imaging, PE=pulmonary embolism, U/S=ultrasound, VQ=ventilation/perfusion VTE=venous thromboembolism

[a]Follow-up time based on median follow-up or when no median was specified, intended study follow up period was used

Supplemental Table 3. Measures of association between VTE and biomarkers in perioperative or hospital setting

Biomarker	**ID[&]**	**Cutpoint**	**Method of Measurement**	**Time of Measurement**	**Effect measure (95% CI)**	**Adjusted effect measure (95% CI)**
Albumin	149	< 34.65 g/L	--	3 days after surgery	OR: 1.39 (1.28-1.52)	OR: 1.01 (0.93-1.09)
	S017	Continuous (g/dL)	--	preoperative	OR: 1.41 (0.18-1.96)	OR: 0.40 (0.16-1.00)
	S017	< 42 g/L	--	preoperative	OR: 2.75 (1.12-6.70)	OR: 2.99 (1.20-7.45)
	S055	< 30 g/L	--	preoperative	--	OR: 1.75 (1.36-2.24)
Antithrombin	S049	Continuous (%)	Amidolytic method	preoperative	RR: 0.74	--
C-Reactive Protein	46	≥ 50 mg/L*	Particle enhanced immunonephelometry on a Behring nephelometer II	preoperative	OR: 1.54 (0.30-7.85)	--
Cancer Antigen 19-9	S051	Continuous (unspecified)	--	preoperative	OR: 1.00 (0.99-1.00)	--
Cancer Antigen 125	S049	Continuous (unspecified)	--	Preoperative	RR: 1.00	--
	S002	Continuous (unspecified)	--	Preoperative	--	OR: 1.36 (0.87-2.13)
	653	> 760 kU/L	--	Preoperative	OR: 4.67 (1.20-17.96)	OR: 21.88 (1.41-330.12)

Creatinine	S054	Yes	--	Preoperative	OR: 0.35 (0.03-3.86)	--
D-dimer	11	Continuous (ug/mL)	--	Day 2 after surgery	OR: 1.12 (1.04-1.22)	OR: 1.12 (1.03-1.21)
	80	0.5 to 1.00 ug/mL > 1.00 ug/mL	--	Preoperative	--	OR: 1.83 (1.19-2.81) OR: 5.04 (2.63-9.64)
	149	> 4.71 ug/mL	--	Preoperative	OR: 1.84 (1.18-2.87)	OR: 1.15 (0.93 – 1.09)
	289	> 0.48 ug/mL	Second-generation latex immunoassay kit	Preoperative	HR: 17.97 (5.64-57.31)	HR: 2.90 (1.05-8.06)
	653	> 0.788 ug/mL	--	Preoperative	OR: 3.49 (1.06-11.49)	OR: 9.83 (1.30 – 74.5)
	787	> 1.9 ug/mL	Latex turbidimetric method	Day after surgery	OR: 19.55 (2.07-184.87)	--
	896	≥ 0.3 ug/mL *	Auto Dimer assay	Preoperative	HR: 3.91 (1.39-11.0)	HR: 6.53 (1.58-27.0)
	S022	≥ 0.5 ug/mL *	Immunoturbidimetry assay	Preoperative	--	OR: 4.44 (0.48-41.34)
	S039	≥ 0.3 ug/mL	--	Preoperative	--	HR: 7.52 (3.97-14.25)
	S049	Continuous (ng/mL)	Enzyme-linked immunosorbent assays	Preoperative	RR: 1.00	--
	S054	>5 ug/mL	--	Preoperative	OR: 3.16 (1.90-5.25)	OR: 2.21 (1.28-3.82)

Erythrocyte Count	11	4.30 x 10^{12}/L	--	At admission	OR: 0.36 (0.14-0.94)	OR: 0.39 (0.15-1.05)
Fibrinogen	S049	Continuous (mg/dL)	Method of Clauss	Preoperative	RR: 1.00	--
Hemoglobin	653	> 104 g/L	--	Preoperative	OR: 3.57 (0.45-28.34)	--
	S022	<100 g/L	--	Preoperative	OR: 2.23 (0.47-10.60)	OR: 4.10 (2.76-6.11)
	S051	<100g/L	--	Preoperative	OR: 0.87 (0.33-2.33)	--
	S057	OR (per 10 g/L)	--	Preoperative	--	OR: 1.27 (1.03-1.56)
Homocysteine	80	Unspecified	--	Preoperative	--	OR: 4.10 (2.76-6.11)
Low-density lipoprotein	S054	>3.36 mmolL	--	Preoperative	OR: 1.13 (0.67-1.90)	--
Lymphocyte Count	S051	Continuous (unspecified)	--	Preoperative	OR: 0.58 (0.42-0.80)	
Mean Platelet Volume	289	> 9.0 fL	Autoanalyzer	Preoperative	HR: 5.19 (1.17-23.01)	HR: 9.45 (1.23-72.44)
miR-130b-3p	50G	Continuous (1sd)	--	Preoperative	--	Standardized OR: 1.08
miR-140-3p	50G	Continuous (1sd)	--	Preoperative	--	Standardized OR: 0.77

miR-22-5p	50G	Continuous (1sd)	--	Preoperative	--	Standardized OR: 0.99
miR-222-3p	50G	Continuous (1sd)	--	Preoperative	--	Standardized OR: 0.88
miR-363-3p	50G	Continuous (1sd)	--	Preoperative	--	Standardized OR: 0.85
miR-451a	50G	Continuous (1sd)	--	Preoperative	--	Standardized OR: 0.94
miR-885-5p	50G	Continuous (1sd)	--	Preoperative	--	Standardized OR: 0.99
miR-93-3p	50G	Continuous (1sd)	--	Preoperative	--	Standardized OR: 0.91
Monocyte Count	702	>0.484 x 10^9/L	ADVIA120 automated hematology analyzer	At admission	OR: 5.27 (1.95-14.3)	OR: 5.0 (1.62-15.5)
	702	>0.8 x 10^9/L	ADVIA120 automated hematology analyzer	At admission	OR: 2.86 (1.28-6.38)	--
Neutrophil Count	702	$\geq$ 7.7 x 10^9/L	ADVIA120 automated hematology analyzer	At admission	OR: 1.97 (0.89-4.37)	--
Neutrophil Lymphocyte Ratio	S051	>3	--	Preoperative	OR: 1.83 (1.05-3.19)	--

Plasma viscosity	S050C	Continuous (mPas)	Capillary tube viscosimeter	Preoperative	RR: 4448 (9.8-2010000)	--
	S050O	Continuous (mPas)	Capillary tube viscosimeter	Preoperative	RR: 6.7 (1.39-1134)	--
Plasminogen activator inhibitor activity	S049	Continuous (U/mL)	--	Preoperative	RR: 0.98	--
Platelet Count	149	<198 x10^9/L	--	Preoperative	OR: 1.33 (0.91-1.94)	--
	653	>261 x10^9/L	--	Preoperative	OR: 4.22 (1.12-15.89)	--
	702	$\geq$ 350 x 10^9/L	ADVIA120 automated hematology analyzer	At admission	OR: 1.55 (0.68-3.5)	--
	S002	continuous (unspecified) per 50 increase	--	Preoperative	OR: 1.22 (1.04-1.43)	OR: 1.01 (1.002-1.01)
	S022	>400 x 10^9/L	--	Preoperative	OR: 2.62 (0.32-21.86)	OR: 7.43 (0.43-128.12)
	S055	>400 x 10^9/L	--	Preoperative	OR: 1.96 (1.57-2.45)	OR: 1.64 (1.30-2.07) (compared to 150-400 x10^9/L as reference)

Platelet Lymphocyte Ratio	S037	> 320 x 10^9/L	--	Preoperative	OR: 96.0 (13.2-1134.5)	--
	S051	>260 x10^9/L	--	Preoperative	OR: 2.03 (1.08-3.81)	OR: 3.56 (1.40-9.05)
Protein C	S049	Continuous (%)	Amidolytic method	Preoperative	RR: 0.09	--
Prothrombin time	653	>11.7 sec	--	Preoperative	OR: 5.67 (1.48-21.81)	OR: 7.63 (1.23-47.12)
Red Blood Cell aggregate low shear	S050	Continuous	Photometric rheoscop	Preoperative	RR: 1.08 (1.02-1.15)	
Total cholesterol	S054	>5.17 mmol/L	--	Preoperative	OR: 1.18 (0.69-2.01)	--
Triglycerides	S054	>1.7 mmol/L	--	Preoperative	OR: 1.03 (0.59-1.81)	--
Tumor marker CA153	S049	Continuous (unspecified)	--	Preoperative	RR: 0.74	--
Tumor marker CA724	S049	Continuous (unspecified)	--	Preoperative	RR: 1.005	--
Tumor marker CEA	S049	Continuous (unspecified)	--	Preoperative	RR: 0.99	--
Uric acid	S054	yes	--	Preoperative	OR: 0.01 (0.00-0.02)	--
White Blood Count	653	>5.4 x 10^9/L†	--	Preoperative	OR: 1.91 (0.57-6.43)	--
	702	≥11 x 10^9/L	ADVIA120 automated hematology analyzer	At admission	OR: 1.97 (0.9-4.31)	--

	S022	>10 x 10^9/L	--	Preoperative	OR: 6.47 (1.62-25.88)	OR: 17.96 (2.45-131.87)

Abbreviations: CI=Confidence Interval, HR=Hazard Ratio, OR=Odds Ratio, RR=Relative Risk

* categorization was based on a pre-existing cut-off and was not determined from the data of the study

[&] When stratified results are presented in the study, the first letter of the cancer group was given with the study ID to differentiate the groups (G=glioma, M=Meningioma, C=Cervical, O=Ovarian)

[†]Value in study was incorrect (i.e., not plausible, not consistent with raw data) and was corrected accordingly

Supplemental Table 4. Measures of central tendency[1] between incident VTE and no VTE in perioperative or hospitalized cancer patients

Biomarker	**ID[&]**	**Unit**	**VTE**			**No VTE**			***p-value***
			Mean (+/- SD)	Median (IQR)	Range	Mean (+/- SD)	Median (IQR)	Range	
Activated Partial Thromboplastin time	46	sec	--	29.7		--	29.1	--	*0.654*
	50G	ratio	--	0.77 (0.69-0.82)		--	0.84 (0.77-0.93)	--	*0.0139*
	50M	ratio	--	0.95 (0.86-1.03)		--	0.94 (0.85-1.01)	--	*0.8262*
	144	sec	28.96 (1.5)	--	--	29.26 (0.46)	--	--	*0.901*
	149	sec	26.7 (6.2)	--	(20.1-43.6)	28.9 (6.8)	--	(16.3-54.3)	*0.154*
	S020	sec	--	31.2	(22.9-37.6)	--	29.6	(18.1-43.3)	*0.342*
	5515	sec	--	29.3	(24.2-31.5)	--	27.9	(20-43.2)	*0.93*
	S054	sec	22.78 (3.16)	--	--	34.17 (3.62)	--	--	*0.002*
Alanine Transaminase	5515	IU/L	--	17	(10-28)	--	17	5-68	*0.85*
	S054	IU/L	26.65 (27.53)	--	--	24.19 (22.10)	--	--	*0.616*

Albumin	149	g/L	40.7 (4.3)	--	(33.8-48.4)	42.1 (5.2)	--	(24.9-64.6)	*0.179*
	5515	g/L	--	36	(30-41)	--	39	(22-48)	*0.33*
	S057	g/L	--	39 (34-42)	--	--	41 (37-43)	--	*0.12*
Aspartate Aminotransferase	5515	IU/L	--	21	(16-30)	--	20	(10-90)	*0.7*
C-Reactive Protein	46	mg/L	--	6 (1-35)	--	--	1.00 (1.00-11)	--	*0.518*
	50G	mg/L	--	0.06 (0.03-0.24)	--	--	0.07 (0.03-0.19)	--	*0.6419*
	50M	mg/L	--	0.13 (0.06-0.29)	--	--	0.09 (0.06-0.24)	--	*0.5331*
	S020	mg/L	--	0.3	(0-8)	--	0.7	(0-110)	*0.342*
	5515	mg/L		1.2	(0.3-10.9)	--	2	(2-335)	*0.99*
Cancer Antigen 125	290	IU/L	--	32.2 (80)	--	--	22.3 (47)	--	*0.173*
	S002	unspecified	2750.4 (4559.3)	--	--	1424.1 (2655)	--	--	*0.163*
Calprotectin	50G	mg/L	--	2051	--	1368	--	--	*0.06*
Creatinine	5515	Mg/dL	--	0.7	(0.47-0.94)	--	0.79	(0.51-5.09)	*0.6*
D-dimer	50G	mg/L	--	0.295 (0.128-0.725)	--	--	0.193 (0.186-0.288)	--	*0.2895*

	50M	mg/L	--	0.183 (0.108-0.243)	--	--	0.165 (0.088-0.206)	--	*0.6063*
	144	mg/L	2.31 (0.56)	--	--	0.71 (0.07)	--	--	*0.002*
	149	mg/L	3.3 (1.7)	--	(0.2-5.79)	2.7 (3.5)	--	(0.1-22.49)	*0.021*
	289	mg/L	1.24 (1.77)	--	--	0.48 (0.15)	--	--	*<0.001*
	S020	mg/L	--	1.00	(0.5-4.9)	--	0.7	(0.4-24.1)	*0.796*
	368 - day 1 postop	mg/L	2.55 (2.8)	--	--	1.2 (1.3)	--	--	*0.001*
	368	mg/L	0.89 (2.3)	--	--	0.42 (0.6)	--	--	*0.05*
	787 – day 1 postop	mg/L	1.88 (0.746)	--	--	0.89 (0.105)	--	--	*0.0009*
	5515	mg/L	--	1.3	(0.2-2.9)	--	0.6	(0.1-9.2)	*0.17*
Eosinophil Count	702 - at hospitalization admission	$x10^9/L$	0.192 (0.254)	--	--	0.117 (0.257)	--	--	*0.138*
Estimated glomerular filtration rate	50G	mL/min per $1.73m^3$	--	86.5 (74.8-107)	--	--	99.8 (81.2-121.1)	--	*0.2644*
	50M	mL/min per $1.73m^3$	--	91.9 (76.3-113.9)	--	--	90.9 (78.3-97.8)	--	*0.8136*

Endogenous thrombin potential	446	nM*min	--	3.21 (7.02)	--	--	2.70 (7.92)	--	*<0.05*
Fibrinogen	46	g/L	--	4.47	--	--	4.25	--	*0.665*
	50G	g/L	--	2.29 (1.97-2.71)	--	--	2.23 (1.86-2.88)	--	*0.7419*
	50M	g/L	--	2.57 (2.39-2.96)	--	--	2.57 (2.14-3.10)		*0.6877*
	144	g/L	3.5 (0.35)	--	--	2.9 (0.07)	--	--	*0.067*
	149	g/L	3.90 (1.10)	--	(2.56-7.04)	3.60 (1.20)	--	(1.58-8.15)	*0.145*
	S008	g/L	5.38 (1.58)	--	--	5.11 (2.26)	--	--	--
	S048	g/L	3.93 (1.41)	--	--	3.78 (1.09)	--	--	--
	S054	g/L†	2.84 (0.95)	--	--	2.61 (0.76)	--	--	--
Hematocrit	S008	%	38.1 (5.1)	--	--	36.6 (5.3)	--	--	--
	S048	%	38.5 (6.07)	--	--	41.1 (3.00)	--	--	*0.09*
Hemoglobin	49	g/L	--	113 (105-131)	--	--	126 (113-135)	--	*0.002*
	50G	g/L	--	141 (125-151)	--	--	136 (127-148)	--	*0.648*
	50M	g/L	--	130 (118-142)	--	--	129 (120-139)	--	*0.7053*
	289	g/L†	131.6 (6.2)	--	--	134.5 (12.5)	--	--	*0.407*
	702 – at hospitalization admission	g/L	109 (198)	--	--	110 (22)	--	--	*0.242*

	S008	g/L	132 (17)	--	--	123 (16)	--	--	--
	S020	g/L	--	118	(90-147)	--	119	(89-149)	*0.637*
	5515	g/L	--	124	(108-135)	--	127	(73-168)	*0.37*
	S057	g/L	--	130 (114-141)	--	--	121 (100-139)	--	*0.064*
International normalized ratio	S054	--	0.93 (0.05)	--	--	0.94 (0.13)	--	--	*0.847*
International normalized ratio (quick)	46	--	--	1.07	--	--	0.97	--	*0.344*
Lag-time	446	sec	--	180.6 (88.2)	--	--	226.8 (96)	--	*>0.05*
Lymphocyte Count	49	$x10^9/L$	--	1.6 (1.3-2.1)	--	--	1.8 (1.3-2.3)	--	*0.266*
	702 – at hospitalization admission	$x10^9/L$	1.6 (0.91)	--	--	1.29 (0.93)	--	--	*0.397*
	5515	$x10^9/L$	--	1.33	(0.68-2.14)	--	1.52	(0.27-4.04)	*0.49*
	S037	$x10^9/L$	0.9 (0.51)	--	--	1.7 (0.72)	--	--	*0.7689*
Mean Corpuscular Volume	702 – at hospitalization admission	fL	83.8 (9.68)	--	--	84.2 (9.43)	--	--	*0.873*

Mean Platelet Volume	289	fL	8.00 (1.00)	--	--	9.1 (1.50)	--	--	*0.003*
Monocyte Count	702 – at hospitalization admission	$x10^9/L$	0.759 (0.312)	--	--	0.555 (0.416)	--	--	*0.013*
Myeloperoxidase	50G	ng/mL	--	118.5	--	75.7	--	--	*0.028*
Neutrophil Count	49	$x10^9/L$	--	4.5 (3.6-6.7)	--	--	4.7 (3.5-6.3)	--	*0.964*
	50G	$x10^9/L$	--	6.52 (5.26-7.63)	--	--	5.6 (3.85-7.18)	--	*0.1345*
	50M	$x10^9/L$	--	3.64 (3.01-5.95)	--	--	3.66 (2.84-4.41)	--	*0.4203*
	702 – at hospitalization admission	$x10^9/L$	10 (6.19)	--	--	8.79 (7.34)	--	--	*0.237*
	5515	$x10^9/L$	--	3.18	(2.65-5.72)	--	3.01	(0.979-18.42)	*0.47*
Nucleosomes	50G	U	--	0.35	--	0.22	--	--	*0.23*
Peak Thrombin	446	nM	--	327.7 (73.1)	--	--	288.8 (87.3)	--	*>0.05*
plasma cell free DNA	50G	ng/mL	--	1180	--	--	1146	--	*0.31*
plasma viscosity	S008	Ns/m^2	0.00147 (0.001)	--	--	0.00138 (0.002)	--	--	*0.04*

	S048	Ns/m^2	0.0014 (0.0011)	--	--	0.00133 (0.001)	--	--	--
Plasmin inhibitor-plasmin complex	144	ug/mL	1.33 (0.26)	--	--	0.59 (0.04)	--	--	*0.0001*
Platelet Count	49	$x10^9/L$	--	287 (242-361)	--	--	279 (232-244)	--	*0.794*
	50G	$x10^9/L$	--	225 (206-252.5)	--	--	227 (179.5-247)	--	*0.5366*
	50M	$x10^9/L$	--	263 (214.5-306.8)	--	--	208.5 (167.5-234.8)	--	*0.0029*
	149	$x10^9/L$	279.8 (103.3)	--	103-449	265.4 (116.7)	--	65-935	*0.496*
	289	$x10^9/L$	256.3 (63.4)	--	--	237.1 (51.6)	--	--	*0.172*
	702 – at hospitalization admission	$x10^9/L$	305 (123)	--	--	275 (176)	--	--	*0.385*
	S002	$x10^9/L$	396.8 (137.9)	--	--	315.4 (133.4)	--	--	*0.004*
	S008	$x10^9/L$	331 (157)	--	--	350 (173)	--	--	--
	S020	Unspecified	--	25.1	15.1-50.6	--	29	12.5-54.2	*0.692*
	5515	$x10^9/L$	--	153	(22-211)	--	167	(133-501)	*0.81*

	S037	x10^9/L	265.4 (108.3)	--	--	231.7 (70.7)	--	--	*0.4252*
	S054	x10^9/L	206.52 (52.73)	--	--	210.68 (59.33)	--	--	*0.575*
	S057	x10^9/L	--	237 (180-297)	--	--	204 (126-274)	--	*0.082*
Platelet distribution width	289	%	16.5 (2.1)	--	--	16.7 (1.5)	--	--	*0.595*
Platelet Lymphocyte Ratio	S037	ratio	130.11	--	--	77.39	--	--	*0.0002*
Prothrombin fragment 1+2	1108	nmol/L	Unclear whether mean(SD) or median (IQR): 2.01 (1.72-2.36)		--	Unclear whether mean(SD) or median (IQR): 1.75 (11.62-1.90)		--	--
Prothrombin time	50G	ratio	--	0.97 (0.92-1.10)	--	--	0.99 (0.93-1.09)		*0.5271*
	50M	ratio	--	1.01 (0.99-1.06)	--	--	1.04 (0.97-1.09)	--	*0.5968*
	144	sec	11.68 (0.15)	--	--	11.78 (0.12)	--	--	--
	149	sec	10.9 (1.1)	--	9.4-13.6	11.1 (1.4)	--	8-16.7	*0.589*
	S020	ratio	--	0.91	0.84-1.02	--	0.91	0.79-1.1	*0.57*
	5515	%	--	11.9	11.3-100	--	12.2	10.2-120.5	*0.67*

	S054	%	125.38 (24.57)	--	--	131.52 (31.64)	--	--	*0.063*
	S054	sec	10.73 (0.58)	--	--	10.77 (1.41)	--	--	*0.813*
Red Blood Cell Aggregation (low shear)	S008	--	32.9 (7.4)	--	--	32.2 (6.8)	--	--	--
	S050B	--	--	32.8 (28.5-35)	--	--	26.1 (23.2-32.1)	--	*<0.05*
Red Blood Cell Aggregation (stasis)	S008	--	18.1 (6.1)	--	--	16.8 (4.3)	--	--	--
	S050B	--	--	17.8 (14.3-19.8)	--	--	15.9 (11.7-18.9)	--	*<0.05*
Soluble Fibrin	1108	ug/L	7.77 (5.22-11.56)	--	--	4.55 (3.55-5.84)	--	--	--
Soluble Fibrin Polymers	1158	ug/mL[b]	9.3 (2.6)	--	--	1.9 (0.5)	--	--	*0.02*
Thrombin Time	46	sec	--	17.6	--	--	17.6	--	*0.996*
	144	sec	17.21 (0.38)	--	--	17.81 (0.09)	--	--	*0.133*
	149	sec	17.7 (1.7)	--	14.7-19.9	17.7 (1.6)	--	12.4-25.2	*0.981*
	S054	sec	18.94 (1.28)	--	--	18.94 (1.43)	--	--	*0.992*
Thrombin-antithrombin complex	144	ug/L	3.28 (0.78)	--	--	1.71 (0.14)	--	--	*0.004*
	1108	ug/L	Unclear whether mean (SD) or median (IQR): 3.83 (3.07-4.78)		--	Unclear whether mean (SD) or median (IQR): 3.72 (3.30-4.19)		--	--

Thrombomodulin	144	TU/mL	8.1 (0.45)	--	--	9.7 (0.76)	--	--	*0.505*
Tissue to Peak	446	min	--	5.7 (1.9)	--	--	6.57 (1.72)	--	*>0.05*
tissue factor microparticles activity	399	mg/L	--	0.0027 (0.00117-0.00312)	--	--	0.00072 (0.000085-0.00107)	--	--
tissue plasminogen activator-plasminogen activator inhibitor-1 complex	144	ng/mL	0.0073 (0.0013)	--	--	0.00599 (0.00024)	--	--	*0.416*
Total Bilirubin	5515	mg/dL	--	0.4	0.78-1.25	--	0.6	0.2-1.86	*0.52*
White blood count	49	$x10^9/L$	--	7.1 (6.1-9.3)	--	--	7.5 (6.0-9.2)	--	*0.902*
	50G	$x10^9/L$	--	10.9 (8.8-12.7)	--	--	9.3 (6.4-12)	--	*0.1283*
	50M	$x10^9/L$	--	6 (5-9.6)	--	--	6.1 (4.7-7.3)	--	*0.4851*
	289	$x10^9/L$	5.73 (1.42)	--	--	6.09 (1.78)	--	--	*0.443*
	702 – at hospitalization admission	$x10^9/L$	12.6 (6.64)	--	--	10.8 (7.81)	--	--	*0.838*
	S008	$x10^9/L$	7.8 (1.9)	--	--	7.9 (3.2)	--	--	--
	5515	$x10^9/L$	--	4.6	3.8-7.7	--	5.3	2.2-22.2	*0.78*

	S037	$x10^9/L$	8.6 (2.47)	--	--	6.98 (2.21)	--	--	*0.0659*
	S054	$x10^9/L$	6.94 (2.39)	--	--	6.8 (2.53)	--	--	*0.649*
	S057	$x10^9/L$	--	6.8 (5.5-8.6)	--	--	6.3 (4.4-9.2)	--	*0.52*

Abbreviations: IQR=interquartile range, SD=standard deviation, VTE=venous thromboembolism

[&] When stratified results are presented in the study, the first letter of the cancer group was given with the study ID to differentiate the groups (G=glioma, M=Meningioma, B=Breast)

[1]Measures were done preoperatively unless otherwise stated

[†]Value in study was incorrect (ie. not plausible, not consistent with raw data) and was corrected accordingly

Supplemental Table 5. Measures of association between VTE and biomarkers

Biomarker	**ID[&]**	**Cutpoint**	**Method of Measurement**	**Time of Measurement**	**Effect measure (95% CI)**	**Adjusted effect measure (95% CI)**
50% Lysis	157	Continuous – per doubling (min)	--	at cancer diagnosis	SHR: 0.83 (0.57-1.22)	--
Acquired Activated Protein C Resistance	3872	Acquired vs normal	Method reported by Ronde and Bertina	at cancer diagnosis	OR: 0.62 (0.08-5.02)	--
Activated Glycoprotein IIb/IIIa	360	Continuous - per decile (%)	--	at cancer diagnosis	HR: 0.97 (0.77-1.23)	--
Activated Glycoprotein IIb/IIIa activated by glycoprotein VI	360	Continuous - per decile (%)	--	at cancer diagnosis	HR: 0.79 (0.59-1.02)	--
Activated Glycoprotein IIb/IIIa activated by Protease-activated -1	360	Continuous - per decile (%)	--	at cancer diagnosis	HR: 0.76 (0.57-0.97)	--

Activated Glycoprotein IIb/IIIa activated by Protease-activated-4	360	Continuous - per decile (%)	--	at cancer diagnosis	HR: 0.9 (0.71-1.13)	--
Activated Partial Thromboplastin time ratio	S021	<0.96	--	pre-chemotherapy	OR: 2.53 (0.75-8.50)	--
ADAMTS-13 activity	460	Continuous (% activity)	FRETS-VWF73 assay	pre-chemotherapy	OR: 1.00 (0.90-1.10)	--
ADAMTS-13 antigen	460	Continuous (ng/mL)	Immubind ADAMTS-13 enzyme-linked immunoassay	pre-chemotherapy	OR: 1.00 (0.90-1.10)	--
Albumin	452	< 44.2 g/L	--	at cancer diagnosis	SHR: 2.05 (1.14-3.69) OR: 2.10 (1.15-3.84)	SHR: 2.17 (1.09-4.32)
	4961	≥ reference limit	Enzyme-linked immunoassay kits or machine-automatized complete blood count	at cancer diagnosis	OR: 2.16 (1.05-4.46)	--
	5083	< 4 g/dL	--	within one week of starting androgen	OR: 0.71 (0.28-1.79)	--

				receptor-signaling inhibitors		
Alkaline phosphatase	5083	≥129 U/L	--	within one week of starting androgen receptor-signaling inhibitors	OR: 0.35 (0.11-1.11)	--
Amplitude	157	Continuous – per doubling	--	at cancer diagnosis	SHR: 1.16 (0.77-1.73)	--
Antithrombin	247	≥87 % activity	Commercially available assays	at cancer diagnosis	OR: 2.33 (0.50-10.80)	--
	256	Continuous (%)	--	at chemotherapy initiation	OR: 0.82 (0.66-1.56)	--
Baseline optical density	157	Continuous – per doubling	--	at cancer diagnosis	SHR: 0.90 (0.58-1.39)	--
Blood glucose	S023	>200 mg/dL	--	at initial clinical evaluation of cancer	OR: 1.62 (1.05-2.50)	--
C-Reactive Protein	397	Continuous (mg/dL)	--	pre-chemotherapy	HR: 1.06 (0.95-1.05)	--

	563	Continuous (mg/dL)	--	at cancer diagnosis	SHR: 1.11 (0.91-1.35)	SHR: 1.08 (0.90-1.31)
	815	>1.8 mg/dL	Immuno-nephelometric assay	at cancer diagnosis	HR: 1.20 (1.00-3.80)	HR: 1.10 (1.00-1.30)
	4961	>2.0 mg/dL	Enzyme-linked immunoassay kits or machine-automatized complete blood count	at cancer diagnosis	OR: 2.75 (1.29-5.84)	OR: 1.01 (1.00-1.01)
Cancer Antigen 19-9	385	≥35 IU/L	--	at cancer diagnosis	HR: 7.20 (1.40-37.90)	HR: 9.50 (1.50-60.2)
	397	Continuous (U/mL)	--	pre-chemotherapy	HR: 0.88 (0.73-1.07)	--
	S023	48-500 U/mL >500 U/mL	--	at cancer diagnosis	OR: 0.77 (0.41-1.41) OR: 1.00 (0.60-1.80)	--
Cancer Antigen 72-4	397	Continuous (U/mL)	--	pre-chemotherapy	HR: 1.10 (0.89-1.36)	--
Cancer Antigen-125	364	≥35 IU/L	--	at the time of nonalcoholic fatty liver diagnosis	OR: 9.33 (4.84-18.03) or HR: 8.51 (4.53-16.00)	HR: 3.81 (1.78-8.17)

	493	>35 IU/L	--	at cancer diagnosis	HR: 2.52 (1.33-4.76)	HR: 2.38 (1.11-5.07)
Carbonic anhydrase 9	5059	Continuous	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: 0.03 (-0.03-0.18)
Carcinoembryonic antigen	397	Continuous (ng/mL)	--	at cancer diagnosis	HR: 1.13 (0.95-1.36)	--
	4964	≥5 ng/mL	Using chemiluminescence	at cancer diagnosis	--	SHR: 2.67 (1.60-4.46)
	S052	≥5.2 ng/mL	--	at cancer diagnosis	OR: 1.17 (0.64-2.15)	--
cell-free DNA	287	≥442.6 ng/mL	Quant-iT PicoGreen dsDNA Assay Kit	at cancer diagnosis	OR: 1.43 (0.88-2.31) or SHR: 1.36 (0.86-2.14)	--
	589	Continuous – per doubling (Unspecified)	--	at cancer diagnosis	HR: 0.99 (0.90-1.10)	--
Cholinesterase	452	Continuous (kU/L)	--	at cancer diagnosis	SHR: 1.01 (1.00-1.01)	SHR: 1.00 (0.99-1.01)
Chromogranin	5083	≥120 ng/mL	--	within one week of starting androgen	OR: 0.45 (0.17-1.18)	--

				receptor-signaling inhibitors		
Citrullinated Histone H3	287	≥88.3 ng/mL	Using a tailor-made capture enzyme-linked immunoassay method	at cancer diagnosis	OR: 2.01 (1.27-3.16) or SHR: 1.76 (1.14-2.72)	SHR (per 100 increase): 1.13 (1.04-1.22)
Clot lysis time	157	Continuous – per doubling (min)	--	at cancer diagnosis	SHR: 0.77 (0.48-1.24)	--
Complete Blood Count	S023	>11 k/uL	--	at cancer diagnosis	OR: 1.54 (0.77-3.08)	--
D-Dimer	139	>2.1 ug/mL	particle-enhanced immunoturbidimetric assay INNOVANCE® D-DIMER on the Behring coagulation system analyser	pre-chemotherapy	OR: 8.09 (1.43-45.52)	--
	247	≥2.1 ug/mL	commercially available assays	at cancer diagnosis	OR: 2.52 (0.82-7.69)	--
	256	Continuous (ug/mL)	--	at chemotherapy initiation	OR: 0.92 (0.63-1.33)	--
	385	≥2.16 ug/mL	STA-LIAtest D-DI quantitative latex assay on a STA-R analyzer	at cancer diagnosis	HR: 5.80 (1.30-26.10)	HR: 4.90 (1.00-23.1)

	397	Continuous ($x10^9$/L)	--	pre-chemotherapy	HR: 1.40 (1.07-1.84)	HR: 1.32 (1.00-1.75)
	477	>1.484 ug/mL	--	at cancer diagnosis	HR: 0.36 (0.14-0.57)	RR: 0.53 (0.28-0.78)
	526	≥75th percentile	--	at cancer diagnosis	OR: 2.55 (1.69-3.84)	--
	708	≥1.32 ug/mL	--	at cancer diagnosis	--	HR: 2.20 (1.30-3.90)
	803	>1 ug/mL	STA-LIAtest D-DI quantitative latex assay	at cancer diagnosis	--	--
	3437	>1.50 ug/mL	Automated latex enhanced turbidimetric immunoassay	pre-chemotherapy	OR: 1.91 (0.69-5.23) HR: 10.10 (4.80-21.30)	HR: 11.0 (2.62-46.2)
	4943	≥1.6 mg/L*	--	3 weeks post-op	SHR: 2.32 (1.28-4.20)	SHR: 2.83 (1.36-5.91)
	4964	≥1.4 ug/mL	Immunoturbidimetric method	at cancer diagnosis	--	SHR: 7.50 (4.49-12.86)
	704	>75th percentile	HemosIL d-dimer HS500 - automated latex enhanced turbidimetric immunoassay was	pre-chemotherapy	HR: 3.00 (1.70-7.20)	HR: 2.70 (1.10-6.80)

			performed using an ACL-TOP automated coagulometer			
	S003	0.262-0.650 ug/mL >0.650 ug/mL	Instrumentation Laboratory Immunometric Rapid Test	pre-chemotherapy	OR: 1.00 (0.06-17.22) OR: 10.04 (1.21-83.46)	-- HR: 4.04 (1.22-13.3)
	S031	Continuous (ug/mL)	--	at cancer diagnosis	HR: 1.06 (1.04-1.09)	HR: 1.06 (1.03-1.09)
	336	≥1.5 ug/mL	Lateximmunoassay kits	pre-chemotherapy	OR: 1.51 (0.36-6.26)	--
	S052	≥1.7 ug/mL	STA-LIAtest D-Di assay	at cancer diagnosis	OR: 12.61 (6.17-25.79)	--
Endogenous thrombin potential	247	≥1087 nM*min	TF 5 pM PPP-Reagent® using the Calibrated Automated Thrombogram-Thrombinosope ® assay	at cancer diagnosis	OR: 0.25 (0.07-0.83)	--
	256	Continuous (nM/min)	Calibrated Automated Thrombogram assay	at chemotherapy initiation	OR: 1.00 (0.998-1.001)	--
Erythrocyte sedimentation rate	4961	Continuous (mm/h)	Enzyme-linked immunoassay kits or machine-automatized complete blood count	at cancer diagnosis	OR: 1.76 (0.78-4.02)	--

Estimated Glomerular filtration rate	452	Continuous – per 1.73m^2 (mL/min)	--	at cancer diagnosis	SHR: 1.03 (0.97-1.08)	SHR: 1.03 (0.88-1.20)
	631	Continuous – per 1.73m^2 (mL/min)	--	pre-chemotherapy	OR: 0.50 (0.15-1.62)	--
Factor V	247	≥103 % activity	Commercially available assays	at cancer diagnosis	OR: 0.15 (0.02-1.18)	--
	256	Continuous (%)		at chemotherapy initiation	OR: 0.92 (0.54-1.43)	--
Factor VII activity	247	≥56.8 ng/mL	Commercially available assays	at cancer diagnosis	OR: 0.34 (0.07-1.59)	--
	256	Continuous (U/mL)	STA-R analyzer	at chemotherapy initiation	OR: 0.99 (0.95-1.02)	--
Factor VIII	287	Continuous – per 1 SD (%)	--	at cancer diagnosis	SHR: 1.23 (1.06-1.42)	--
	469	Continuous – per 100% increase (% activity)	--	at cancer diagnosis	SHR: 1.39 (1.17-1.65)	HR: 1.04 (1.01-1.08)
	475	>261 %	STA® – Deficient VIII kit	pre-chemotherapy	HR: 3.16 (1.40-7.00)	HR: 3.60 (1.60-8.00)
	3872	elevated (2.36 for below 50 age and	--	at cancer diagnosis	OR: 1.38 (0.47-4.08)	--

		2.80 for over equal 50)				
Factor VIII activity	241	Continuous – per doubling (% activity)	Coagulometry	at cancer diagnosis	HR: 2.21 (1.53-3.18)	SHR: 1.53 (1.26-1.87)
Fasting blood glucose	325	>103 mg/dL	--	pre-chemotherapy	OR: 4.21 (2.09-8.46)	HR: 3.56 (1.51-8.39)
Fibrin monomer	247	≥8.4 ug/mL	Commercially available assays	at cancer diagnosis	OR: 2.07 (0.61-6.95)	--
	256	Continuous (ug/mL)	--	at chemotherapy initiation	OR: 0.93 (0.62-12.45)	--
Fibrinogen	241	Continuous – per doubling (mg/dL)	--	at cancer diagnosis	HR: 1.54 (0.99-2.39)	SHR: 1.21 (1.00-1.47)
	397	Continuous ($x10^9$/L)	--	pre-chemotherapy	HR: 1.13 (0.34-3.80)	--
Folate receptor	5059	Continuous	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: 0.03 (-0.03-0.20)
Gamma Globulin level	4770	≥27 g/L	--	at cancer diagnosis	--	OR: 2.80 (1.20-6.80)
Granulocyte colony-stimulating factor	5059	Continuous	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: -0.03 (-0.18-0.03)

Growth Differentiation Factor 15	4823	>2290.9 pg/mL	Roche Elecsys assay on Cobas® e411 platform	1-month after treatment initiation	OR: 1.74 (0.85-3.58)	OR: 1.65 (0.89-3.08) or SHR: 1.60 (0.91-2.83)
Growth Hormone	5059	Continuous (ng/mL)	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: 0.10 (-0.02-0.59)
Hemoglobin	13	<100 g/L	--	pre-chemotherapy	OR: 2.08 (0.99-4.37)†	--
	241	Continuous – per doubling (g/dL)	Sysmex XE systems	at cancer diagnosis	HR: 0.51 (0.22-1.17)	SHR: 0.87 (0.72-1.03)
	274	<100 g/L	--	at cancer diagnosis	OR: 1.00 (0.33-3.06)	--
	336	<100 g/L	--	pre-chemotherapy	OR: 1.35 (0.26-6.97)	--
	397	Continuous (g/dL)	--	pre-chemotherapy	HR: 0.96 (0.79-1.16)	--
	631	<100 g/L	--	pre-chemotherapy	OR: 2.71 (0.58-12.71)	--
	862	Unclear (g/dL)	--	pre-chemotherapy	OR: 1.09 (0.79-1.50)	--

	4964	<115 g/L	--	at cancer diagnosis	--	SHR: 2.20 (1.38-3.53)
	5059	<100 g/L	--	pre-chemotherapy	OR: 0.59 (0.18-1.92)	--
	5083	≤125 g/L	--	within one week of starting androgen receptor-signaling inhibitors	OR: 1.18 (0.45-3.08)	--
	S009	<100 g/L	--	pre-chemotherapy	--	HR: 2.31 (1.52-3.51)
	S014	<100 g/L	--	pre-chemotherapy	OR: 1.64 (0.53-4.99)	HR: 1.54 (0.43-5.50)
	S016	<100 g/L	--	pre-chemotherapy	OR: 5.33 (0.71-40.35)	--
	S023	≤100 g/L	--	at cancer diagnosis	OR: 2.32 (0.96-5.65)	OR: 3.18 (1.14-8.85)
	S038	<100 g/L	--	at cancer diagnosis	OR: 1.31 (0.36-4.82)	--
	S043	<100 g/L	--	pre-chemotherapy	OR: 1.16 (0.57-2.35)	--

	S046	<100 g/L	--	pre-chemotherapy	--	SHR: 0.76 (0.32-1.80)
	S051	<100 g/L	--	pre-chemotherapy	OR: 2.35 (0.95-5.80)	--
	S052	<100 g/L	--	at cancer diagnosis	OR: 2.17 (1.18-3.97)	--
	S056	<100 g/L	--	pre-chemotherapy	OR: 0.65 (0.22-1.89)	OR: 0.29 (0.06-1.43)
	S058	<100 g/L	--	pre-chemotherapy	OR: 0.65 (0.22-1.89)	--
Heparanase	256	Continuous (ng/mL)	R&D Systems	at chemotherapy initiation	OR: 0.02 (0.001-46.07)	--
Heparin-binding EGF-like growth factor	5059	Continuous	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: 0.03 (-0.03-0.20)
High sensitivity troponin T	4823	>14 pg/mL	Roche Elecsys assay on Cobas® e411 platform	at 1 month after treatment initiation	OR: 2.35 (1.07-5.17)	OR: 2.26 (1.40-3.65) or SHR: 2.15 (1.37-3.35)
HOMA index	325	>2.6	--	pre-chemotherapy	OR: 3.57 (1.51-8.44)	HR: 4.13 (1.63-10.5)

					HR: 3.17 (1.61-6.23)	
Homocysteine	862	Unclear (%)	Enzymatic assay	pre-chemotherapy	OR: 0.94 (0.85-1.04)	
Human chorionic gonadotropin Beta	5059	Continuous (miU/mL)	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: 0.03 (-0.03-0.23)
Human epidermal growth factor receptor 2	5059	Continuous (ng/mL)	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: 0.04 (-0.03-0.35)
Interferon-inducible T-cell alpha chemoattractant	5059	Continuous	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: 0.10 (-0.02-0.72)
Interleukin-1 receptor type 1	5059	Continuous (pg/mL)	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: 0.03 (-0.03-0.25)
Interleukin-10	589	Continuous – per doubling	--	at cancer diagnosis	HR: 1.01 (0.83-1.22)	--
Interleukein-11	589	Continuous – per doubling	--	at cancer diagnosis	HR: 0.90 (0.76-1.06)	--
Interleukin-1b	589	Continuous – per doubling	--	at cancer diagnosis	HR: 0.98 (0.80-1.20)	--

Interleukin-3	589	Continuous – per doubling	--	at cancer diagnosis	HR: 0.99 (0.84-1.18)	--
Interleukin-4	589	Continuous – per doubling	--	at cancer diagnosis	HR: 1.11 (0.86-1.42)	--
Interleukin-6	493	5-19.9 pg/mL ≥20 pg/mL	Enzyme-linked immunoassay	at cancer diagnosis	HR: 9.66 (1.25-74.9) HR: 12.1 (1.50-95.5)	HR: 7.98 (0.99-64.0) HR: 8.90 (1.04-76.0)
	589	Continuous – per doubling	--	at cancer diagnosis	HR: 1.08 (0.98-1.20)	--
Interleukin-8	589	Continuous – per doubling	--	at cancer diagnosis	HR: 1.06 (0.94-1.20)	--
Lactate Dehydrogenase	631	≥ 300 IU/L	--	pre-chemotherapy	OR: 1.25 (0.26-6.01)	--
	1021	elevated	--	pre-chemotherapy	RR: 4.60 (0.60-37.90)	--
	4961	≥reference limit	Enzyme-linked immunoassay kits or machine-automatized complete blood count	at cancer diagnosis	OR: 2.37 (1.40-4.00)	--
	5083	≥225 U/L	--	within one week of starting androgen	OR: 1.08 (0.39-2.98)	SHR: 1.34 (0.84-2.16)

				receptor-signaling inhibitors		
Lag time	256	Continuous (min)	--	at chemotherapy initiation	OR: 0.60 (0.29-1.24)	--
	157	Continuous – per doubling (sec)	--	at cancer diagnosis	SHR: 1.59 (1.04-2.45)	SHR: 1.34 (0.84-2.16)
Mast/stem cell cell growth factor receptor	5059	Continuous (ng/mL)	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	--
Maximum Clot formation rate	157	Continuous – per doubling (optical density/min)	--	at cancer diagnosis	SHR: 1.10 (0.77-1.58)	--
Maximum Clot lysis rate	157	Continuous – per doubling (min)	--	at cancer diagnosis	SHR: 1.37 (0.93-2.01)	--
Mean Platelet Volume	241	Continuous – per doubling (fL)	Sysmex XE systems	at cancer diagnosis	HR: 0.64 (0.15-2.70)	SHR: 0.94 (0.78-1.14)
	552	<7.3 fL	hematology analyzer - Coulter LH750	pre-chemotherapy	OR: 2.55 (1.11-5.84)	HR: 2.32 (1.03-5.23)
Mean rate index of thrombin generation	247	≥121 Nm/min	TF 5 pM PPP-Reagent® on Calibrated Automated Thrombogram	at cancer diagnosis	OR: 1.40 (0.36-5.49)	

Mean rate index of thrombin generation	256	Continuous	Calibrated Automated Thrombogram assay	at chemotherapy initiation	OR: 1.02 (1.00-1.03)	
MHC class I chain-related protein A	5059	Continuous	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: 0.03 (-0.03-0.23)
Microparticle associated tissue factor activity	S036P	Continuous (pg/mL or fmol Fxa/min) – per doubling	Chromogenic endpoint assay Chromogenic kinetic assay	at cancer diagnosis	HR: 1.60 (1.00-2.50) HR: 1.00 (0.90-1.20)	HR: 1.50 (1.00-2.40) HR: 1.00 (0.80-1.10)
Microparticle associated tissue factor activity	S036B	Continuous (pg/mL or fmol Fxa/min) – per doubling	Chromogenic endpoint assay Chromogenic kinetic assay	at cancer diagnosis	HR: 0.90 (0.70-1.30) HR: 1.10 (1.00-1.30)	HR: 0.90 (0.70-1.30) HR: 1.10 (0.90-1.30)
Microparticle associated tissue factor activity	S036S	Continuous (pg/mL or fmol Fxa/min) – per doubling	Chromogenic endpoint assay	at cancer diagnosis	HR: 0.70 (0.40-1.20)	--
Microparticle associated tissue factor activity	S036C	Continuous (pg/mL or fmol	Chromogenic endpoint assay	at cancer diagnosis	HR: 0.90 (0.60-1.60)	HR: 0.90 (0.60-1.60)

		Fxa/min) – per doubling				
Microvesicle tissue factor activity	385	≥2.37 pg/mL	chromogenic endpoint assay measuring TF-dependent Xa generation	at cancer diagnosis	HR: 4.60 (1.20-17.20)	HR: 10.5 (1.50-72.4)
Monocyte chemotactic protein 4	5059	Continuous (pg/mL)	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: -0.12 (-0.71-0.02)
Monocyte-platelet aggregates	360	Continuous – per decile (%)	--	at cancer diagnosis	HR: 0.88 (0.69-1.10)	--
Monocyte-platelet aggregates by glycoprotein VI	360	Continuous – per decile (%)	--	at cancer diagnosis	HR: 0.79 (0.59-1.00)	--
Monocyte-platelet aggregates by Protease-activated -1	360	Continuous – per decile (%)	--	at cancer diagnosis	HR: 0.78 (0.59-1.00)	--
Monocyte-platelet aggregates by Protease-activated -4	360	Continuous – per decile (%)	--	at cancer diagnosis	HR: 0.85 (0.66-1.07)	--

Monocytes	118	≥0.6 x 10^9/L and ≥0.5 x 10^9/L	--	at cancer diagnosis	OR: 1.91 (0.65-5.64) and OR: 3.01 (0.65-14.06)	--
Myoglobin	5059	Continuous	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: 0.03 (-0.03-0.24)
N-terminal pro-B type natriuretic peptide	4823	>185.3 pg/mL	Roche Elecsys assay on Cobas® e411 platform	at 1 month after inclusion	OR: 1.29 (0.62-2.68)	OR: 1.19 (0.69-2.06) or SHR: 1.15 (0.68-1.94)
Neutrophil Count	13	>1 x 10^9/L	--	pre-chemotherapy	OR: 0.95 (0.21-4.33)	--
	118	≥6.5 x 10^9/L and ≥5.1 x 10^9/L	--	at cancer diagnosis	OR: 2.21 (0.77-6.44) OR: 1.64 (0.55-4.83)	--
	241	Continuous – per doubling (x10^9/L)	Sysmex XE systems	at cancer diagnosis	HR: 1.28 (1.01-1.62)	SHR: 1.19 (1.01-1.40)
	4964	≥7.5 x 10^9/L	--	at cancer diagnosis	--	SHR: 2.33 (1.38-3.96)
	2073	≥5.7 ratio	Sysmex XE-5000 haematology analyser	at cancer diagnosis	OR: 1.19 (0.79-1.78) or	SHR: 1.20 (1.00-1.40)

Neutrophil Lymphocyte Ratio					SHR: 1.20 (1.00-1.40)	
	4961	≥3 ratio	Enzyme-linked immunoassay kits or machine-automatized complete blood count	at cancer diagnosis	OR: 2.50 (1.48-4.21)	OR: 1.04 (1.00-1.09)
	5083	≥3 ratio	--	within one week of starting androgen receptor-signaling inhibitors	OR: 0.94 (0.38-2.35)	--
	S014	>3 ratio	Coulter LH750 hematology analyzer	pre-chemotherapy	HR: 1.90 (1.10-3.30) or OR: 1.81 (1.03-3.17)	--
	S015	>3 ratio	--	at cancer diagnosis	HR: 0.80 (0.30-2.50) or OR: 0.81 (0.25-2.57)	--
	S051	>3 ratio	--	pre-chemotherapy	OR: 1.25 (0.76-2.05)	--

Nucleosomes	287	≥3 MoM	Cell Death Detection ELISAPLUS	at cancer diagnosis	OR: 1.12 (0.69-1.84) or SHR: 1.13 (0.70-1.80)	--
P-selectin	247	≥46 700 pg/mL	Enzyme-linked immunoassay Kits from Cusabio	at cancer diagnosis	OR: 2.69 (0.71-10.30)	--
	256	Continuous (ng/mL)	Enzyme-linked immunoassay Kits from Cusabio Biotech	at chemotherapy initiation	OR: 1.00 (1.00-1.00)	--
P-selectin activated by glycoprotein VI	360	Continuous – per decile (%)	Dade-Behring and Human sP-selectin enzyme-linked immunoassay kit, Quantikine®, R&D Systems	at cancer diagnosis	HR: 0.77 (0.59-0.98)	--
P-selectin activated by Protease-activated receptor-1	360	Continuous – per decile (%)	Dade-Behring and Human sP-selectin enzyme-linked immunoassay kit, Quantikine®, R&D Systems	at cancer diagnosis	HR: 0.73 (0.56-0.92)	--
P-selectin activated by Protease-activate receptor-4	360	Continuous – per decile (%)	Dade-Behring and Human sP-selectin enzyme-linked immunoassay kit, Quantikine®, R&D Systems	at cancer diagnosis	HR: 0.89 (0.70-1.12)	--
Peak absorbance	157	Continuous – per doubling	--	at cancer diagnosis	SHR: 1.15 (0.66-2.01)	--

Peak thrombin	247	≥253 nM	TF 5 pM PPP-Reagent® on Calibrated Automated Thrombogram	at cancer diagnosis	OR: 1.50 (0.49-4.61)	--
	256	Continuous (nM)	Calibrated Automated Thrombogram assay (CAT; Diagnostica Stago)	at chemotherapy initiation	OR: 1.01 (1.00-1.02)	--
	S005	≥611 nM	Technothrombin TGA kit, Techonoclone	at cancer diagnosis	HR: 2.00 (1.30-3.20)	--
	S005	Continuous (nM)	Technothrombin TGA kit, Techonoclone	at cancer diagnosis	HR: 1.15 (1.02-1.30)	--
	241	Continuous – per doubling (nM of thrombin)	Technothrombin TGA kit, Technoclone	at cancer diagnosis	HR: 1.03 (0.87-1.23)	SHR: 1.03 (0.86-1.25)
plasma tumor DNA fraction	5083	≥0.175	Quant-iT high sensitivity PicoGreen double-stranded DNA Assay Kit (Invitrogen) or by spectrophotometric evaluation (NanoDrop ND-1000, Celbio)	within one week of starting androgen receptor-signaling inhibitors	OR: 7.25 (2.05-25.60)	SHR: 5.78 (1.63-20.44)
plasmin alpha2-plasmin inhibitor-1	336	<1.8 ug/mL	lateximmunoassay kits	pre-chemotherapy	OR: 7.10 (0.40-126.5)	--

plasminogen activator inhibitor-1	397	Continuous ($x10^9$/L)	--	pre-chemotherapy	HR: 1.20 (0.66-2.17)	--
Platelet Count	13	>350 x 10^9/L	--	pre-chemotherapy	OR: 1.15 (0.63-2.12)	--
	118	≥ 350 x 10^9/L	--	at cancer diagnosis	OR: 0.69 (0.24-2.01)	--
	118	≥ 450 x 10^9/L	--	at cancer diagnosis	OR: 0.99 (0.33-2.92)	--
	241	Continuous – per doubling ($x10^9$/L)	Sysmex XE systems	at cancer diagnosis	HR: 1.37 (0.98-1.93)	SHR: 1.22 (0.99-1.50)
	274	>350 x 10^9/L	--	at cancer diagnosis	OR: 0.75 (0.39-1.43)	--
	336	≥ 350 x 10^9/L	--	pre-chemotherapy	OR: 0.30 (0.00-5.20)	--
	364	≥ 400 x 10^9/L	--	at the time of nonalcoholic fatty liver disease diagnosis	OR: 6.11 (3.28-11.40) or HR: 5.16 (2.94-9.06)	HR: 2.30 (1.22-4.35)
	397	Continuous ($x10^9$/L)	--	pre-chemotherapy	HR: 1.00 (1.00-1.01)	--

	493	≥ 400 x 10^9/L	--	at cancer diagnosis	HR: 1.66 (1.26-2.18)	HR: 1.42 (1.03-1.96)
	563	Continuous (x10^9/L)	--	at cancer diagnosis	SHR: 0.69 (0.51-0.91)	SHR: 0.73 (0.53-0.95)
	631	≥ 130 x 10^9/L	--	pre-chemotherapy	OR: 0.46 (0.12-1.82)	--
	636	≥ 350 x10^9/L	--	pre-chemotherapy	--	HR: 1.70 (0.90-3.10)
	832	Continuous	--	at cancer diagnosis	HR: 0.23	Natural log odds: 0.0003
	858	Continuous – per 50 (x10^9/L)	--	at cancer diagnosis	HR: 1.28 (1.12-1.46)	HR: 1.18 (1.01-1.38)
	858	>443 x 10^9/L	--	at cancer diagnosis	HR: 5.07 (2.35-11.00)	HR: 3.50 (1.52-8.06)
	858	>350 x 10^9/L	--	at cancer diagnosis	HR: 2.42 (1.22-4.80)	HR: 1.63 (0.79-3.37)
	862	≥300 x 10^9/L	--	pre-chemotherapy	OR: 1.60 (1.01-2.52)	OR: 1.66 (1.04-2.64)
	4943	≥196 x 10^9/L	--	3 weeks after surgery	OR: 0.93 (0.45-1.92) or SHR: 1.00 (0.99-1.00)	SHR: 1.00 (0.99-1.00)

	5059	>350 000/uL	--	pre-chemotherapy	OR: 1.15 (0.55-1.92)	--
	S009	≥350 x 10^9/L	--	pre-chemotherapy	--	HR: 1.83 (1.19-2.83)
	S014	>350 x 10^9/L	Coulter LH750 hematology analyzer	pre-chemotherapy	OR: 0.29 (0.07-1.25)	HR: 0.18 (0.03-1.02)
	S016	>350 x 10^9/L	--	pre-chemotherapy	OR: 0.81 (0.28-2.29)	--
	S023	>350 k/uL	--	at cancer diagnosis	OR: 1.03 (0.59-1.82)	--
	S026	≥350 x 10^9/L	--	pre-chemotherapy	HR: 2.30 (1.40-3.80)	--
	S043	≥350 x 10^9/L	--	pre-chemotherapy	OR: 0.72 (0.47-1.09)	--
	S046	≥350 x 10^9/L	--	pre-chemotherapy	--	SHR: 1.40 (0.80-2.40)
	S051	>443 x10^9/L	--	pre-chemotherapy	OR: 1.48 (0.38-5.69)	--
	S052	≥350 x10^9/L	--	at cancer diagnosis	OR: 3.29 (1.45-7.47)	--
	S056	≥350 x10^9/L	--	pre-chemotherapy	OR: 1.63 (0.96-2.75)	OR: 2.30 (1.09-4.84)

	S058	≥350 x10^9/L	--	pre-chemotherapy	OR: 0.77 (0.35-1.67)	--
Platelet Factor 4	832	>11 kU/mL	Enzyme-linked immmunoassay (Asserchrom, Stago)	at cancer diagnosis	OR: 3.45 (1.35-8.86) or RR: 2.70 or HR: 1.77 or HR (continuous): 1.08	Natural log odds: 0.132
Platelet Lymphocyte Ratio	2073	>264	Sysmex XE-5000 haematology analyser	at cancer diagnosis	OR: 0.92 (0.60-1.40) or SHR: 1.00 (0.80-1.30)	SHR: 1.00 (0.80-1.30)
	4961	≥10	Enzyme-linked immmunoassay kits or machine-automatized complete blood count	at cancer diagnosis	OR: 2.24 (1.31-3.83)	--
	S014	> 260	Coulter LH750 hematology analyzer	pre-chemotherapy	OR: 1.72 (0.93-3.16) or HR: 1.90 (1.00-3.40)	--
	S015	> 260	--	at cancer diagnosis	OR: 0.66 (0.17-2.56) or	--

					HR: 0.80 (0.20-3.10)	
	S051	>260	--	pre-chemotherapy	OR: 0.97 (0.45-2.10)	--
Procoagulant phospholipid dependent clotting time	247	≥47 sec	STA®Procoag-PPL	at cancer diagnosis	OR: 3.49 (1.13-10.82)	--
	256	<44 sec	STA Procoag-PPL (Diagnostica Stago)	at chemotherapy initiation	OR (continuous): 1.06 (1.01-1.14)	OR: 1.09 (1.03-1.19)
Protein C	475	>118 %	STA® – Staclot® Protein C kit	pre-chemotherapy	HR: 2.90 (1.30-6.20)	HR: 2.39 (1.00-5.40)
	477	>75.2 %	--	at cancer diagnosis	RR: 1.97 (1.30-2.58)	RR: 1.11 (0.87-1.34)
	862	Unclear (% activity)	--	pre-chemotherapy	OR: 1.00 (0.98-1.02)	--
Protein S	862	Unclear (% activity)	Immunoturbidimetric assay	pre-chemotherapy	OR: 1.00 (0.98-1.03)	--
Prothrombin fragment F1+2	241	Continuous – per doubling (pmol/L)	Enzyme-linked immunoassay (Enzygnost F 1 2; Dade-Behring)	at cancer diagnosis	HR: 1.50 (1.19-1.88)	SHR: 1.38 (1.15-1.66)
	469	Continuous (pmol/L)	--	at cancer diagnosis	SHR: 1.48 (1.23-1.78)	--

Pulmonary and activation-regulated chemokine	5059	Continuous (ng/mL)	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: -0.03 (-0.25-0.03)
Soluble P-selectin	241	Continuous – per doubling (ng/mL)	Soluble P-selectin Enzyme-linked immmunoassay (R&D Systems)	at cancer diagnosis	HR: 1.40 (1.02-1.93)	SHR: 1.25 (1.01-1.53)
	360	Continuous – per decile (%)	Dade-Behring and Human sP-selectin enzyme-linked immunoassay kit, Quantikine®, R&D Systems	at cancer diagnosis	HR: 0.92 (0.72-1.15)	--
Stromal cell-derived factor 1	5059	Continuous (pg/mL)	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: -0.24 (-0.93-0.02)
Superoxide dismutase 1 soluble	5059	Continuous	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: 0.03 (-0.03-0.20)
Thrombin-antithrombin complex	385	≥6.7 ng/mL	--	at cancer diagnosis	HR: 3.50 (0.80-13.50)	HR: 4.40 (0.70-29.0)
Thrombin-antithrombin III complex	336	≥2.1 ng/mL	chemiluminescent enzyme	Prechemotherapy	OR: 5.33 (1.07-26.65)	--

Thrombomodulin activity	247	≥42 % activity	--	at cancer diagnosis	OR: 4.93 (0.97-25.00)	--
Thrombopoeitin	858	Unclear (pg/mL)	Enzyme-linked immmunoassay kit (Quantikine; R&D Systems)	at cancer diagnosis	HR: 0.99 (0.72-1.35)	--
Thyroid stimulating hormone	5059	Continuous (uIU/mL)	Myriad Human DiscoveryMAP, version 3.3	pre-chemotherapy	--	PM: -0.18 (-0.80-0.02)
Time to maximum clot formation rate	157	>353 sec	--	at cancer diagnosis	OR: 1.37 (0.81-2.32) or SHR: 1.44 (1.00-2.06)	SHR: 1.20 (0.79-1.81)
Time to peak absorbance	157	Continuous – per doubling (sec)	--	at cancer diagnosis	SHR: 1.19 (0.73-1.93)	--
Time to peak thrombin concentration	256	Continuous (min)	Calibrated Automated Thrombogram assay (Diagnostica Stago)	at chemotherapy initiation	OR: 0.52 (0.31-0.89)	--
Tissue factor activity	247	≥0.03 ng/mL	--	Pretreatment	OR: 0.49 (0.09-2.50)	--
	256	Continuous (pM)	homemade test	at chemotherapy initiation	OR: 0.99 (0.91-1.08)	--

Tissue factor bearing microparticles	S042	>3.5 x 10^4/uL	--	within 4 weeks of first or second line therapy	OR: 5.63 (0.80-39.61)	--
Tissue Factor pathway inhibitor	247	≥39 ng/mL	commercially available assays	at cancer diagnosis	OR: 7.75 (1.51-39.7)	--
Total proteins	4961	≥reference limit	Enzyme-linked immmunoassay kits or machine-automatized complete blood count	at cancer diagnosis	OR: 1.91 (1.08-3.39)	--
Tumor necrosis factor alpha	43	Continuous – per doubling (pg/mL)	multiplex immunoassays, Multiplex Bead-Based Kits	at cancer diagnosis	HR: 1.10 (0.70-1.73)	--
Vascular endothelial growth factor	43	Continuous – per doubling (pg/mL)	multiplex immunoassays, Multiplex Bead-Based Kits	at cancer diagnosis	HR: 1.00 (0.64-1.55)	--
Vascular endothelial growth factor A	469	>17.65 (pg/mL)	multiplex immunoassay (xMAP technology from Luminex)	at cancer diagnosis	SHR: 1.18 (1.00-1.39)	HR: 1.04 (1.00-1.09)
Vascular endothelial growth factor D	2064R	≥115 pg/mL	dual-monoclonal sandwich immunoassays	before cycle 1 of respective treatment in pts with disease progression during or within	OR: 0.84 (0.43-1.66)	--

				6 months of last dose of first-line combination therapy		
Vascular endothelial growth factor D	2064P	≥115 pg/mL	dual-monoclonal sandwich immunoassays	before cycle 1 of respective treatment in pts with disease progression during or within 6 months of last dose of first-line combination therapy	OR: 0.54 (0.24-1.19)	--
Velocity index of thrombin generation	241	Continuous – per doubling ()	Technothrombin TGA kit (Technoclone)	at cancer diagnosis	HR: 1.04 (0.93-1.17)	SHR: 1.07 (0.88-1.29)
Von Willebrand factor	460	>290 IU/mL	Asserachrom® vWF:Ag; STAGO	pre-chemotherapy	OR: 4.30 (1.60-11.70)	--
Von Willebrand antigen	477	>192 %	--	at cancer diagnosis	RR: 0.48 (0.26-0.70)	RR: 0.92 (0.68-1.26)

White blood count	13	>11 x 10^9/L	--	pre-chemotherapy	OR: 1.81 (1.01-3.26)	--
	118	≥11 x 10^9/L ≥7.5 x 10^9/L	--	at cancer diagnosis	OR: 2.30 (0.71-7.47) and OR: 2.52 (0.82-7.77)	--
	241	Continuous – per doubling (x10^9/L)	Sysmex XE systems	at cancer diagnosis	HR: 1.07 (0.90-1.29)	SHR: 1.07 (0.91-1.25)
	274	>11 x 10^9/L	--	at cancer diagnosis	OR: 1.21 (0.64-2.29)	--
	336	≥11 x 10^9/L	--	pre-chemotherapy	OR: 0.70 (0-14.00)	--
	397	Continuous (x10^9/L)	--	pre-chemotherapy	HR: 1.00	--
	452	Continuous (x10^9/L) †	--	at cancer diagnosis	SHR: 1.07 (1.01-1.14)	SHR: 1.05 (1.00-1.09)
	563	Continuous (x10^9/L)	--	at cancer diagnosis	SHR: 2.01 (1.09-3.64)	SHR: 1.85 (0.99-3.41)
	636	>11 x10^9/L	--	pre-chemotherapy	--	HR: 1.70 (0.80-3.40)
	858	Continuous – per 2-fold	--	at cancer diagnosis	--	HR: 1.15 (0.63-2.11)

	862	Continuous - unspecified	--	pre-chemotherapy	OR: 0.87 (0.67-1.13)	--
	5059	>11 x 10^9/L	--	pre-chemotherapy	OR: 0.83 (0.36-1.93)	--
	S009	>11 x 10^9/L	--	pre-chemotherapy	OR: 2.58 (1.62-4.12)	HR: 2.10 (1.30-3.40)
	S014	>11 x 10^9/L	Coulter LH750 hematology analyzer	pre-chemotherapy	OR: 0.74 (0.25-2.21)	HR: 0.79 (0.23-2.65)
	S016	>11 x 10^9/L	--	pre-chemotherapy	OR: 0.86 (0.26-2.85)	--
	S038	≥11 x 10^9/L	--	at cancer diagnosis	HR: 5.69 OR: 4.28 (1.08-16.90)	--
	S046	>11 x 10^9/L	--	pre-chemotherapy	--	SHR: 0.87 (0.42-1.80)
	S051	>11 x 10^9/L	--	pre-chemotherapy	OR: 0.94 (0.40-2.21)	--
	S052	≥11 x 10^9/L	--	at cancer diagnosis	OR: 1.70 (0.72-4.04)	--
	S056	>11 x 10^9/L	--	pre-chemotherapy	OR: 2.33 (1.14-4.79)	OR: 1.74 (0.63-4.85)

	S058	>11 x 10^9/L	--	pre-chemotherapy	OR: 0.98 (0.45-2.12)	--

Abbreviations: CI=Confidence Interval, HR=Hazard Ratio, OR=Odds Ratio, PM=Posterior means, RR=Relative Risk

* categorization was based on a pre-existing cut-off and was not determined from the data of the study

[&] When stratified results are presented in the study, the first letter of the cancer group or treatment was given with the study ID to differentiate the groups (B=Brain, P=Pancreatic, S=Stomach, C=Colorectal, R=ramucirumab+5-fluororuracil, P=placebo+5-fluororuracil)

[†]Value in study was incorrect (i.e., not plausible, not consistent with raw data) and was corrected accordingly

Supplemental Table 6. Measures of central tendency between incident VTE and no VTE in cancer patients

Biomarker	**ID[&]**	**Timing of measurement**	**Unit**	**VTE**			**No VTE**			***p-value***
				Mean (+/- SD)	Median (IQR)	Range	Mean (+/- SD)	Median (IQR)	Range	
50% lysis	157	at cancer diagnosis	Min	--	8 (6.4-11.4)	--	--	8.4 (6.6-11.7)	--	*0.35*
Activated partial thromboplastin time	S053	pre-chemotherapy	sec	25.5 (0.8)	--	--	29.71 (1.7)	--	--	--
ADAMTS-13 activity	460	pre-chemotherapy to 1-week after	% Activity	87 (19)	--	--	81 (19)	--	--	*0.2*
ADAMTS-13 antigen	460	pre-chemotherapy to 1-week after	ng/mL	579 (108)	--	--	562 (137)	--	--	*0.6*
Albumin	786	at cancer diagnosis	g/dL	--	4.06	3.36-4.73	--	3.89 (1.67-5.04)	--	--
Amplitude	157	at cancer diagnosis	optical density	--	0.69 (0.51-0.87)	--	--	0.65 (0.49-0.82)	--	*0.48*
Baseline optical density	157	at cancer diagnosis	--	--	0.26 (0.21-0.37)	--	--	0.27 (0.21-0.37)	--	*0.74*

Beta2-microglobulin	786	at cancer diagnosis	mg/L	--	3.68	1.19-38.20	--	3.21	1.05-16.40	--
C-Reactive Protein	786	at cancer diagnosis	mg/L	--	2.7	0-10.8	--	3.3	0-71.7	--
	4961	at cancer diagnosis	mg/L	--	30.6	0.8-251.8	--	9.9	0.1-274.6	*<0.0001*
CA 19-9	385	at cancer diagnosis	U/mL	--	7789 (220-22900)	--	--	194 (56-920)	--	*0.3*
CA 125	364	at diagnosis of fatty liver disease	IU/L	--	142	4-7192	--	17	2-5421	*<0.0001*
Calcium	786	at cancer diagnosis	mmol/L	--	2.41	2.11-3.43	--	2.39	1.97-3.59	--
Calprotectin	163	at cancer diagnosis	ng/mL	--	1374	--	--	427	--	*0.017*
cell-free DNA	163	at cancer diagnosis	ng/mL	--	2048	--	--	1688	--	*0.41*
	287	at cancer diagnosis	ng/mL	--	394.5 (322-461.5)	--	--	355.8 (302-440.7)	--	--
Citrullinated histone H3	287	at cancer diagnosis	ng/mL	--	52.4 (11.8-153)	--	--	24.1 (1.5-84)	--	--

Clot lysis time	157	at cancer diagnosis	min	--	11.1 (9.5-14.5)	--	--	11.7 (9.7-15.6)	--	*0.29*
Creatinine	786	at cancer diagnosis	mg/dL†	--	0.96	0.60-9.55	--	0.60	9.55-1.00	--
D-dimer	139	pre-chemotherapy	ug/mL	--	2.8 (1.5-4.6)	--	--	1.15 (0.58-1.8)	--	*0.031*
	385	at cancer diagnosis	ug/mL	--	2.19 (1.16-3.26)	--	--	0.710 (0.53-1.26)	--	*0.04*
	460	pre-chemotherapy to 1-week after	ug/mL	5.00 (6.60)	--	--	1.60 (2.20)	--	--	--
	532	pre-chemotherapy	ug/mL	Geometric mean: 0.23 (0.17)	--	--	Geometric mean: 0.20 (0.19)	--	--	*0.62*
	3437	pre-chemotherapy	ug/mL	--	3.51	1.55-5.96	--	1.06	0.64-1.64	*0.0002*
	704	pre-chemotherapy	ug/mL	--	1.48	--	--	0.92	--	*0.03*
	S019	pre-chemotherapy	ug/mL	Geometric mean: 1.61 (1.66)	--	--	Geometric mean: 0.72 (0.58)	--	--	*0.003*

	S031	at cancer diagnosis	ug/mL	--	1.08 (0.59-2.34)	--	--	0.67 (0.34-1.32)	--	*<0.001*
	S053	pre-chemotherapy	ug/mL	3.13 (2.39)	--	--	0.96 (0.61)	--	--	--
E-selectin	S019	pre-chemotherapy	ng/mL	31.5 (18.8-52.7)	--	--	29.3 (26.7-32.2)	--	--	*0.7*
Endogenous Thrombin Potential	246	at cancer diagnosis	nM*min	--	1336 (1164-1471)	--	--	1222 (1056-1403)	--	*0.26*
	246	at cancer diagnosis	nM*min	--	1123	--	--	1271 (1118-1427)	--	*0.15*
	S005	at cancer diagnosis	nM	--	4475 (4087-4915)	--	--	4386 (3804-4890)	--	*0.197*
Erythrocyte sedimentation rate	4961	at cancer diagnosis	mm/h	--	38	2-150		26	2-150	*0.023*
Extracellular DNA	385	at cancer diagnosis	ng/mL	--	22 (12.5-34.2)	--	11.9 (4.2-28.8)	--	--	
Extracellular vesicle tissue factor	246	at cancer diagnosis	pg/mL	--	0.14 (0.03-0.62)	--	0.18 (0.06-0.31)	--	--	*0.86*
	246 LMWH	at cancer diagnosis	pg/mL	--	0.15	--	0.21 (0.08-0.32)	--	--	*0.61*
Factor VIII	385	at cancer diagnosis	%	--	200 (154-247)		--	189 (140-225)	--	--

	532	pre-chemotherapy	IU	Geometric mean: 1.71 (1.13-2.91)	--	--	Geometric mean: 1.38 (1.27-1.49)	--	--	*0.69*
	3872	at cancer diagnosis	IU/mL	--	2.59	0.86-5.17		2.22	0.24-7.14	*0.564*
	882	at cancer diagnosis	%	--	211 (168-257)	--	--	177 (135-223)	--	*<0.001*
Fasting blood glucose	325	pre-chemotherapy	mg/dL	122 (53)	--	60-339	105 (36)	--	51-415	*0.019*
Fasting insulin	325	pre-chemotherapy	uIU/mL	--	17.2 (11.9-24.5)	--	--	11.6 (8.7-18.6)	--	*0.016*
Fibrinogen	385	at cancer diagnosis	g/L	--	3.6 (3.3-4.2)		--	3.9 (3.5-4.6)	--	
	4961	at cancer diagnosis	g/L†	--	5.7	1.9-11.8	--	5.3	1.00-13.2	*0.351*
	S008	pre-chemotherapy	g/L	5.51 (1.12)	--	--	4.62 (1.58)	--	--	--
	S019	pre-chemotherapy	g/L	Geometric mean: 5.1 (2.8-7.5)	--	--	Geometric mean: 3.4 (3.2-3.7)	--	--	*0.004*
	S048	pre-chemotherapy	g/L	5.89 (1.24)	--	--	4.62 (1.26)	--	--	*<0.05*

	S053	pre-chemotherapy	g/L	4.2 (0.65)	--	--	3.65 (1.14)	--	--	--
Free tissue factor pathway inhibitor	385	at cancer diagnosis	ng/mL	--	17.2 (14.5-25.5)	--	--	16 (11.7-23.5)	--	
Growth Differentiation Factor 15	4823	1-month after start of treatment	pg/mL	--	2352 (2726)	--	--	1909 (2066)		*0.2031*
Growth Hormone	5059	pre-chemotherapy	ng/mL	--	1.6	0.1-16	--	0.8	0.1-28	*0.006*
Hematocrit	S008	pre-chemotherapy	%	33.8 (4.2)	--	--	32.2 (4.2)	--	--	
Hemoglobin	385	at cancer diagnosis	g/L	--	132 (116.5-146)	--	--	131 (116-143)	--	--
	460	pre-chemotherapy to 1-week after	g/L	128 (21)	--	--	129 (19)	--	--	--
	786	at cancer diagnosis	g/L	--	105	77.5-138	--	110.7	65.4-152	--
	862	pre-chemotherapy	g/L	--	130	110-160	--	130	80-160	--
	4961	at cancer diagnosis	g/L	--	117	87-141	--	123	51-172	*0.017*

	S008	pre-chemotherapy	g/L	114 (14)	--	--	110 (14)	--	--	
	S015	at cancer diagnosis	g/L	106 (27)	--	--	112 (19)	--	--	*0.408*
	S031	at cancer diagnosis	g/L	--	131 (115-142)	--	--	131 (118-141)	--	*0.66*
	S051	pre-chemotherapy	g/L	128.5 (19.5)	--	--	129.3 (17.0)	--	--	*0.694*
	S053	pre-chemotherapy	g/L	111.99 (11.92)	--	--	112.63 (10.80)	--	--	--
Hemoglobin 1AC	S038	at cancer diagnosis	%	6.2 (0.6)	--	5.2-8	6.1 (0.8)	--	4.3-13	*0.436*
High sensitivity troponin T	4823	1-month after start of treatment	pg/mL	--	8.54 (13.08)	--	--	6.12 (7.3)	--	*0.0674*
Homocysteine	862	pre-chemotherapy	%	--	11.2	5.8-20.9	--	12.2	4.7-75.0	--
Human chorionic gonadotropin Beta	5059	pre-chemotherapy	miU/mL	--	2.2	2.2-279	--	2.2	2.2-252	*0.045*
Human epidermal growth factor receptor 2	5059	pre-chemotherapy	ng/mL	--	0.5	0.2-1.10	--	0.4	0.1-3.6	*0.027*

Immature platelet function	139	pre-chemotherapy	%	--	2.3 (1.9-4.9)	--	--	2.8 (X)	--	*0.815*
Immunoglobulin at urea	786	at cancer diagnosis	g/L	--	0	0-6.2	--	0	0-14.3	--
Interleukin-1 receptor type 1	5059	pre-chemotherapy	pg/mL	--	1940	285-3930	--	1630	175-3470	*0.027*
Interleukin-16	5059	pre-chemotherapy	pg/mL	--	296	129-1120	--	334	135-2200	*0.043*
Interleukin-6	385	at cancer diagnosis	pg/mL	--	11 (0-14.2)	--	--	3.1 (0.2-7.6)	--	--
	493	at cancer diagnosis	pg/mL	--	14.4	--	--	7.1	--	*0.003*
International normalized ratio	S053	pre-chemotherapy	--	1.02 (0.02)	--	--	1.02 (0.07)	--	--	--
Lactate dehydrogenase	786	at cancer diagnosis	ucat/L	--	3.7	1.93-8.15	--	3.5	1.57-30.89	--
Lag time	S005	at cancer diagnosis	min	--	8 (7-10)	--	--	9 (7-11)	--	*0.036*
Lymphocyte Count	118	at cancer diagnosis	$x10^9/L$	--	1.4	0.4-2.8	--	1.7	0.5-3.9	*0.401*
	S015	at cancer diagnosis	--	--	1.8 (1.25)	--	--	1.5 (1)	--	*0.057*

	S051	pre-chemotherapy	$x10^9$/L	1.94 (0.77)	--	--	2.12 (1.61)	--	--	*0.308*
mast/stem cell growth factor receptor	5059	pre-chemotherapy	ng/mL	--	6.3	2.8-15	--	7.4	2.6-15	*0.04*
Maximum Clot Formation Rate	157	at cancer diagnosis	optical density/min	--	0.31 (0.23-0.41)	--	--	0.31 (0.24-0.39)	--	*0.77*
Maximum Clot lysis rate	157	at cancer diagnosis	min	--	0.08 (0.05-0.10)	--	--	0.07 (0.05-0.09)	--	*0.06*
Mean Platelet Volume	139	pre-chemotherapy	fL	--	9.7 (9.2-11)	--	--	10	--	*0.633*
	552	pre-chemotherapy	fL	8.2 (1.1)	--	--	8.6 (1.1)	--	--	*0.0022*
Microparticle associated tissue factor	622	at cancer diagnosis	pg/mL	3.07 (5.2)	--	--	1.4 (1.5)	--	--	*0.01*
Microparticle tissue factor activity	385	at cancer diagnosis	g/L	--	2.23 (0.84-4.26)	--	--	0.61 (0.44-1.48)	--	*0.03*
Monoclonal immunoglobulin at serum	786	at cancer diagnosis	g/L	--	31	0-50.3	--	38.1	0-101	*0.43*

Monocyte chemotactic protein 4	5059	pre-chemotherapy	pg/mL	--	145	33-473	--	183	33-883	*0.017*
Monocyte Count	118	at cancer diagnosis	%	--	0.7	0.3-1.7	--	0.5	0.3-1.2	*0.042*
myeloperoxidase	163	at cancer diagnosis	ng/mL	--	98	--	--	87	--	*0.059*
N-terminal pro-B-type natriuretic peptide	4823	1-month after start of treatment	pg/mL	--	175 (179)	--	--	11.8 (181.34)	--	*0.1013*
Neutrophil Count	118	at cancer diagnosis	$x10^9$/L	--	6.5	3.2-23.6	--	5.1	1.8-27.4	*0.036*
	163	at cancer diagnosis	$x10^9$/L	6.6 (3.6)	--	--	6.1 (2.5)	--	--	*0.65*
	S015	at cancer diagnosis	--	--	5.1 (4.4)	--	--	4.2 (3.7)	--	*0.239*
	S051	pre-chemotherapy	$x10^9$/L	--	5.0 (3.9-6.3)	--	--	4.6 (3.6-5.9)	--	*0.942*
Neutrophil Lymphocyte Ratio	4961	at cancer diagnosis	ratio	--	3.79	0.7-160.5	--	2.7	0.2-32.5	*0.001*
	S051	pre-chemotherapy	ratio	--	2.58 (1.74-3.68)	--	--	2.46 (1.67-3.67)	--	*0.474*

Nucleosomes	163	at cancer diagnosis	U	--	0.12	--	--	0.096	--	*0.25*
	287	at cancer diagnosis	MoM	--	1.3 (0.6-3.2)	--	--	1.2 (0.5-3.0)	--	
P-selectin	5059	pre-chemotherapy	%	--	85	33-340	--	73	36-197	*0.129*
Peak Absorbance	157	at cancer diagnosis	optical density	--	1.03 (0.85-1.17)	--	--	0.96 (0.8-1.16)	--	*0.4*
Peak thrombin generation	246	at cancer diagnosis	nM	--	236 (176-277)	--	--	217 (176-261)	--	*0.42*
	385	at cancer diagnosis	nM	--	218 (165-264)	--	--	213 (174-244)	--	
	S005	at cancer diagnosis	nM	--	556 (432-677)	--	--	499 (360-603)	--	*0.014*
Placenta growth factor	5059	pre-chemotherapy	pg/mL	--	32.5	32.5-123	--	32.5	32.5-82	*0.035*
Plasma viscosity	S008	pre-chemotherapy	mPas	1.36 (0.1)	--	--	1.35 (0.1)	--	--	--
	S048	pre-chemotherapy	mPas	1.37 (0.1)	--	--	1.35 (0.13)	--	--	--
Platelet Count	118	at cancer diagnosis	$x10^9/L$	--	407	107-914	--	378	31-792	*0.779*

	364	at diagnosis of fatty liver disease	x10^9/L	--	--	--	--	--	--	--
	385	at cancer diagnosis	x10^9/L	--	160 (145-262)	--	--	232 (175-330)	--	--
	460	pre-chemotherapy to 1-week after	x10^9/L	317 (117)	--	--	296 (128)	--	--	--
	786	at cancer diagnosis	x10^9/L	--	207	24.4-281	--	201	50-449	--
	862	pre-chemotherapy	x10^9/L	--	259.5	131-412	--	218	79-489	--
	4961	at cancer diagnosis	x10^9/L	--	283	103-678	--	248	29-613	*0.034*
	S008	pre-chemotherapy	x10^9/L	363 (107)	--	--	372 (100)	--	--	
	S015	at cancer diagnosis	x10^9/L	--	328 (220)	--	--	264 (120)	--	*0.421*
	S031	at cancer diagnosis	x10^9/L	--	236 (193-307)	--	--	247 (196-310)	--	*0.75*
	S051	pre-chemotherapy	x10^9/L	252.44 (91.98)	--	--	253.26 (91.98)	--	--	*0.941*

	S053	pre-chemotherapy	$x10^9/L$	312.00 (95.34)	--	--	288.92 (109.45)	--	--	--
Platelet Lymphocyte ratio	4961	at cancer diagnosis	ratio	--	14.5	483.3	--	10.1 (0.3-193.3)		*0.001*
	S051	pre-chemotherapy	ratio	--	121 (88-192)	--	--	123 (88-184)	--	*0.82*
Procoagulant Phospholipids	246	at cancer diagnosis	sec	--	36 (29.4-40.2)	--	--	34 (28.4-40.2)	--	*0.88*
	246 LWMH	at cancer diagnosis	sec	--	37.1	--	--	33.6 (28-39.8)	--	*0.19*
Protac-induced coagulation inhibition percentage	736	pre-chemotherapy	%	77.3 (9.7)	80.1 (73.2-83)	41.7-88.5	77 (11.4)	79 (72.6-84.7)	36.4-93.4	--
Protein C	862	pre-chemotherapy	% activity	--	105.5	16-158		104	25-176	--
Protein S	862	pre-chemotherapy	% activity	--	96	39-118	--	88	24-164	--
Prothrombin Fragment F1+2	460	pre-chemotherapy to 1-week after	pmol	439 (223)	--	--	425 (781)	--	--	--

	892	at cancer diagnosis	pmol/L	--	310	213-416	--	249	190-353	--
Prothrombin time	S053	pre-chemotherapy	sec	13.03 (1.63)	--	--	12.14 (1.71)	--	--	--
Pulmonary and activation-regulated chemokine	5059	pre-chemotherapy	ng/mL	--	157.5	62-849	--	197	51-1090	*0.036*
Red blood cell aggregate low shear	S008	pre-chemotherapy	low shear	31.8 (5.6)	--	--	33.5 (7.6)	--	--	--
Red blood cell aggregate stasis	S008	pre-chemotherapy	stasis	16.9 (3.7)	--	--	16.9 (4.3)	--	--	--
Soluble P-selectin	139	pre-chemotherapy	ng/mL	--	49 (34.8-83.5)	--	--	46	--	*0.68*
	385	at cancer diagnosis	ng/mL	--	33 (27-52)	--	--	28 (23-36)	--	--
	460	pre-chemotherapy to 1-week after	ng/mL	48 (23)	--	--	41 (26)	--	--	--
	S006	at cancer diagnosis	ng/mL	--	45.9 (35.4-62.8)	--		42.1 (32.9)	--	*0.025*

Stromal cell derived factor 1	5059	pre-chemotherapy	pg/mL	--	2550	162-4340	--	2890	1220-5640	*0.003*
Thrombin-antithrombin complex	385	at cancer diagnosis	ng/mL	--	6.6 (4.5-8.3)	--	--	3.5 (2.8-5.6)	--	*0.02*
	532	pre-chemotherapy	ug/mL	3.43 (0-37.50)	--	--	2.18 (1.65-2.89)	--	--	*0.05*
Thyroid stimulating hormone	5059	pre-chemotherapy	uIU/mL	--	0.9	0.02-6.4	--	1.5	0.02-15	*0.006*
Time to maximum clot formation	157	at cancer diagnosis	sec	--	308 (254-377)	--	--	289 (237-352)	--	*0.06*
Time to peak absorbance	157	at cancer diagnosis	sec	--	556 (476-639)	--	--	529 (467-603)	--	*0.18*
Time to peak thrombin - Thrombin generation	246	at cancer diagnosis	min	--	9.1 (7.4-11.2)	--	--	10 (8.4-11.9)	--	*0.26*
	246 LMWH	at cancer diagnosis	min		9.7			9.8 (8.7-11.2)		*0.87*
	S005	at cancer diagnosis	min	--	11.5 (9.5-14)	--	--	13 (11-16)	--	*0.006*
Total tissue factor	246	at cancer diagnosis	a.u.	--	5.1 (4.5-5.1)	--	--	4.8 (4.5-5.1)	--	*0.03*

	246 - LMWH	at cancer diagnosis	a.u	--	4.8	--	--	4.8 (4.6-5.1)	--	--
Vascular endothelial adhesion molecule I	S019	pre-chemotherapy	ng/mL	820 (680-989)	--	--	636 (593-682)	--	--	*0.04*
Vascular endothelial cell growth factor A	469	at cancer diagnosis	pg/mL	27.5 (74.5)	9.4 (1.8-25)	0-512.3	17 (34.6)	8.1 (0-17.5)	0-397.2	*0.03*
Velocity index of thrombin generation	S005	at cancer diagnosis	nM/min	--	160 (111-123)	--	-	127 (71-183)	--	*0.004*
Von Willebrand factor	385	at cancer diagnosis	%	--	283 (167-300)	--	--	223 (158-396)	--	
	460	pre-chemotherapy to 1-week after	IU/mL	326 (185)	--	--	242 (158)	--	--	*0.02*
White Blood Count	118	at cancer diagnosis	$x10^9$/L	--	8.9	4.5-27.3	--	7.3	3.1-29.3	*0.05*
	163	at cancer diagnosis	$x10^9$/L	8.6 (3.2)	--	--	8.7 (2.5)	--	--	*0.92*

	385	at cancer diagnosis	x10^9/L	--	7.2 (6.6-8.8)	--	--	7.2 (6.6-8.9)	--	--
	460	pre-chemotherapy to 1-week after	x10^9/L	8.4 (3.1)	--	--	8.3 (3.1)	--	--	--
	862	pre-chemotherapy	x10^9/L	--	6	4-10	--	6	3-16	--
	4961	at cancer diagnosis	x10^9/L	--	8.5	4.6-16.6	--	7.4	0.4-28.5	*0.132*
	S008	pre-chemotherapy	x10^9/L	6.6 (1.6)	--	--	7.1 (1.6)	--	--	--
	S009	pre-chemotherapy	x10^9/L	8	--	--	9.6	--	--	--
	S031	at cancer diagnosis	x10^9/L	--	7.5 (6.2-10.5)	--	--	7.2 (5.6-9.6)	--	*0.02*
	S051	pre-chemotherapy	x10^9/L	7.69 (3.1)	--	--	7.86 (4.1)	--	--	*0.838*
	S053	pre-chemotherapy	x10^9/L	7.88 (3.1)	--	--	6.58 (2.52)	--	--	--

Abbreviations: IQR=interquartile range, SD=standard deviation, VTE=venous thromboembolism

[&] When stratified results are presented in the study, the first letter of the cancer group was given with the study ID to differentiate the groups (LMWH=low-molecular weight heparin)

[†]Value in study was incorrect (ie. not plausible, not consistent with raw data) and was corrected accordingly

Supplemental Table 7. ROB for each domain of included studies

ID – First author	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall
11 - Dranichnikov	low	low	high	high	low	low	high
13 - Rupa - Matysek	low	low	low	low	low	low	low
43 - Nazari	low	unsure	low	low	low	low	low
46 - Rink	low	unsure	low	high	moderate	low	moderate
49 - Norris	low	low	moderate	low	moderate	low	low
50 - Oto	low	unsure	moderate	low	high	moderate	high
80 - Li	low	unsure	high	low	low	moderate	moderate
109 – Posch	low	unsure	low	low	high	low	moderate
118 – Lopez-Salazar	low	low	low	moderate	high	low	moderate
139 – Schorling	low	moderate	low	low	high	low	moderate
144 - Liang	low	unsure	low	moderate	moderate	low	moderate
149 - Zhou	low	unsure	moderate	low	moderate	low	moderate

157 – Posch	low	low	low	low	low	low	low
163 – Oto	low	unsure	low	low	moderate	low	low
241 – Pabinger	low	low	low	low	low	low	low
246 – Gezelius	low	unsure	low	high	moderate	high	high
247 – Fotiou	low	low	low	low	low	moderate	low
256 – Syrigos	low	low	low	low	moderate	low	low
274 - Munoz-Martin	low	unsure	high	low	moderate	low	moderate
287 - Mauracher	low	moderate	low	low	moderate	low	low
289 - Cui	low	unsure	low	low	high	low	moderate
290 - Matsuo	low	low	low	low	moderate	moderate	moderate
325 – Guadagni	low	unsure	low	high	low	moderate	moderate
336 – Kitayama	low	low	low	low	moderate	moderate	moderate
360 – Riedl	low	unsure	low	low	high	low	moderate
364 - Moeini	low	unsure	moderate	low	low	low	low
368 - Wang	low	unsure	moderate	low	high	low	moderate
385 – Faille	low	unsure	low	low	low	low	low

397 – Park	low	low	high	low	moderate	low	moderate
399 - Unruh	moderate	unsure	low	high	high	high	high
446 - Saadeh	low	unsure	low	low	moderate	low	low
452 – Konigsbrugge	low	unsure	high	low	moderate	low	moderate
460 - Pépin	low	unsure	low	low	low	low	low
469 – Posch	low	unsure	low	low	low	low	low
475 – Tafur	low	low	low	low	moderate	low	low
477 – Jianlong	low	low	low	low	low	low	low
493 – Matsuo	low	unsure	low	low	low	low	low
526 – Ay	low	unsure	low	low	moderate	low	low
532 – Kovacs	low	high	low	moderate	moderate	low	high
552 – Ferroni	moderate	low	low	low	low	moderate	low
563 – Thaler	low	unsure	low	low	moderate	low	low
589 – Reitter	low	unsure	low	low	low	low	low
622 - Bharthuar	low	unsure	low	moderate	moderate	low	moderate
631 – Bagratuni	low	unsure	low	low	moderate	moderate	moderate
636 – Dickmann	low	low	low	low	moderate	low	low

653 - Wu	low	unsure	high	low	low	low	low
702 - Rojnuckarin	low	unsure	low	low	moderate	low	low
704 - Moeini	low	low	low	low	low	low	low
708 – Ahlbrecht	low	moderate	low	low	low	low	low
736 – Ferroni	low	unsure	low	low	low	low	low
786 - Almasi	low	unsure	moderate	high	moderate	low	high
787 - Kusunoki	low	low	low	low	high	low	moderate
803 – Hoke	low	low	low	low	moderate	moderate	moderate
815 – Kanz	low	unsure	low	low	low	low	low
832 – Poruk	moderate	unsure	low	low	low	low	low
858 – Simanek	low	unsure	low	low	low	low	low
862 - Mandala	low	unsure	low	low	high	low	moderate
882 - Vormittag	low	moderate	low	low	low	low	low
892 - Ay	low	moderate	low	low	low	low	low
896 - Stender	low	moderate	low	low	moderate	low	low

1021 – Piektty	low	unsure	moderate	low	moderate	moderate	moderate
1029 – Streetly	low	unsure	low	high	moderate	low	moderate
1108 - Iversen	moderate	unsure	low	low	high	low	moderate
1158 - Sonaglia	moderate	unsure	low	low	high	moderate	high
2064 – Tabernero	low	moderate	low	high	moderate	low	high
2073 – Grilz	low	unsure	low	low	low	low	low
3437 – Ferroni	moderate	low	low	low	moderate	moderate	moderate
3872 – Cini	low	high	moderate	high	moderate	low	high
4708 – Gardini	low	moderate	high	high	moderate	low	high
4770 - Pépin	low	moderate	moderate	high	high	low	high
4823 - Roy	low	low	low	low	low	low	low
4943 - Huang	low	unsure	high	high	low	low	high
4961 - Otasevic	low	unsure	moderate	moderate	moderate	moderate	high
4964 - Li	low	unsure	moderate	low	moderate	low	moderate

5059 – Khorana	low	unsure	low	low	low	low	low
5083 – Conteduca	low	unsure	moderate	moderate	low	low	moderate
5515 - Kaida	low	unsure	moderate	low	low	low	low
S002 - Albertin	low	low	low	low	low	moderate	low
S003 – Arpaia	low	moderate	low	low	moderate	low	low
S005 – Ay	low	unsure	low	low	low	low	low
S006 - Ay	low	low	low	low	low	low	low
S008 – Von Tempelhoff	low	unsure	low	low	high	low	moderate
S009 – Connolly	low	unsure	low	high	moderate	low	moderate
S014 – Ferroni	low	unsure	low	high	low	moderate	moderate
S015 – Fuentes	low	low	low	low	low	low	low
S016 – Rupa-Matysek	low	unsure	low	low	low	low	low
S017 - Khan	low	unsure	high	moderate	low	low	moderate

S019 - Kirwan	moderate	low	low	low	high	low	moderate
S020 - Kodama	low	unsure	low	low	moderate	low	low
S021 - Kruger	low	unsure	low	high	moderate	low	moderate
S022 - Lee	low	high	low	low	moderate	low	moderate
S023 – Li	low	unsure	low	low	low	low	low
S026 - Mansfield	low	unsure	low	low	moderate	low	low
S031 – Posch	low	unsure	low	low	moderate	low	low
S036 – Thaler	low	unsure	low	low	low	low	low
S037 - Tham	low	low	low	low	moderate	low	low
S038 - Wang	low	low	low	low	moderate	low	low
S039 - Yang	low	low	moderate	moderate	moderate	moderate	high
S042 – Zwicker	low	unsure	low	low	high	moderate	moderate
S043 – Kuderer	low	unsure	low	low	low	low	low
S046 – Van Es	low	low	low	low	low	low	low

S048 - Von Tempelhoff	high	unsure	low	low	high	low	high
S049 - Von Tempelhoff	moderate	unsure	low	low	high	moderate	high
S050 - Von Tempelhoff	low	moderate	low	low	moderate	moderate	moderate
A1 – Wang	low	low	low	low	moderate	low	low
S051 - Boone	low	low	low	low	moderate	low	low
S052 - Chen	low	low	low	low	moderate	low	low
S053 - Kuk	high	low	low	moderate	low	low	moderate
S054 - Shi	low	unsure	moderate	low	low	low	low
S055 - Merkow	low	low	low	low	low	low	low
S056 - Yu	low	low	low	high	low	moderate	moderate
S057 - Sinnamon	low	unsure	low	low	high	moderate	moderate
S058 - Sanfilippo	low	low	low	low	moderate	low	low

Supplemental Table 8. Sensitivity analysis of median/mean differences in biomarker levels between VTE and non-VTE occurring within 1 year only (excluding studies with over 1 year of follow-up)

Biomarkers	N of studies	Sample size	VTE	I^2, %	Median difference/ **Mean difference**	*P-value*
AT CANCER DIAGNOSIS						
Peak thrombin (nM)	2	168	21	0	13.06 (-27.01-53.14)	*0.5229*
PRE-CHEMOTHERAPY						
D-dimer (ug/mL)[a]	4	471	54	0	1.75 (1.14-2.45)	*<0.0001* *
Hemoglobin (g/L)	2	586	107	0	**-0.84 (-4.90-3.23)**	*0.6875*
Mean Platelet Volume (fL)	2	678	50	0	-0.39 (-0.73--0.05)	*0.0226**
Platelet Count ($x10^9$/L)	2	586	107	0	2.07 (-18.12-22.25)	*0.8409*
Soluble P-Selectin[b]	2	233	26	0	6.67 (-3.83-17.16)	*0.2131*
White Blood Count ($x10^9$/L)	2	586	107	0	**0.10 (-0.59-0.79)**	*0.7764*
PREOPERATIVE						
Activated Partial Thromboplastin Time (sec)	4	926	116	39.2	-0.73 (-2.34-0.89)	*0.3800*

Alanine transaminase (IU/L)	2	618	78	0	1.09 (-4.66-6.84)	*0.7105*
Albumin (g/L)	3	614	47	0	-1.68 (-3.38-0.02)	*0.0530*
C-Reactive Protein (mg/L)	4	490	66	0	0.01 (-0.06-0.08)	*0.7800*
D-dimer (ug/mL)	5	768	92	15.8	0.08 (-0.05-0.22)	*0.2354*
Quantitative latex-enhanced immunoassay[a]	1	234	15	NA	0.76 (-0.14-1.66)	*0.0964*
Latex photometric immunoassay[c]	1	75	21	NA	0.30 (-0.37-0.97)	*0.3782*
Not stated	3	459	56	0	0.03 (-0.04-0.10)	*0.3980*
Fibrinogen (g/L)[d]	3	825	124	0	**0.14 (-0.03-0.31)**	*0.0989*
Hemoglobin (g/L)	5	790	100	7.5	-1.06 (-4.68-2.56)	*0.5658*
Neutrophil Count (x10^9/L)	2	226	39	0	0.38 (-0.55-1.30)	*0.4221*
Platelet Count (x10^9/L)	7	1547	195	57.6	**20.94 (0.68-41.21)**	*0.0428**
Prothrombin time (ratio)	2	175	55	0	-0.01 (-0.04-0.02)	*0.4069*
Prothrombin time (sec)	2	233	17	0	**-0.20 (-0.76-0.36)**	*0.4802*
Prothrombin time (%)	2	618	78	0	-5.97 (-12.27-0.34)	*0.0635*
Thrombin time (sec)	2	725	90	0	0.00 (-0.30-0.30)	*1.0000*
White Blood Count (x10^9/L)	5	1207	152	0	0.04 (-0.38-0.46)	*0.8552*

Statistically significant ($p<0.05$*)

[a]D-dimer levels for the included studies were measured via quantitative latex-enhanced immunoturbidimetric immunoassay (cut-off for the assay: 0.5 ug/mL).

[b]Soluble P-selectin measured using human sP-selectin Immunoassay from R&D Systems Inc.

[c]D-dimer levels measured via latex photometric immunoassay (cut-off for the assay: 1.0 ug/mL).

[d]Method of measurement not stated.

Supplemental Table 9. Sensitivity analyses of the OR of dichotomous biomarker cut-offs with VTE occurring within 1 year in cancer patients (excluding studies with over 1 year of follow-up)

Biomarkers	**Cut-off**	**Included studies**	**Sample size**	**VTE**	**I^2, %**	**Pooled OR**	***P-value***
PRE-CHEMOTHERAPY							
Hemoglobin (g/L)	<100	7	6089	453	33.5	1.01 (0.67-1.52)	*0.9761*
Platelet Count (x10^9/L)	≥ 350	5	5463	354	0	0.75 (0.55-1.04)	*0.0811*
Platelet Lymphocyte Ratio	≥ 260	2	1236	141	22.1	1.36 (0.79-2.35)	*0.2742*
White Blood Count (x10^9/L)	> 11	7	10294	534	58.9	1.10 (0.70-1.74)	*0.6860*
PREOPERATIVE							
Hemoglobin (g/L)	<100	2	800	73	28.3	0.99 (0.52-1.89)	*0.9816*
Platelet Count (x10^9/L)	≥ 400	2	45056	731	0	1.97 (1.58-2.46)	*<0.0001**

Statistically significant ($p<0.05$*)

Supplemental Table 10. Sensitivity analyses of median or mean differences in biomarker levels between VTE and non-VTE patients when measured at cancer diagnosis, pre-chemotherapy or preoperatively (excluding studies that screened for VTE)

Biomarkers	N of studies	Sample size	VTE	I^2, %	Median difference/ **Mean difference**	*P-value*
AT CANCER DIAGNOSIS						
D-dimer (ug/mL)[a]	2	1726	154	60.4	0.75 (-0.23-1.72)	*0.1326*
Factor VIII (% activity)	2	881	71	0	31.50 (11.55-51.45)	*0.0020**
Fibrinogen (g/L)[b]	2	747	78	52.8	0.05 (-0.64-0.73)	*0.8983*
Hemoglobin (g/L)	4	2544	236	51.1	-3.48 (-8.69-1.73)	*0.1900*
Peak thrombin (nM)	3	1201	98	0	29.82 (-1.71-61.34)	*0.0638*
Platelet Count ($x10^9$/L)	4	2551	239	65.2	-0.82 (-41.68-40.04)	*0.9687*
Soluble P-Selectin[c]	2	728	53	0	4.02 (-2.85-10.89)	*0.2513*
Time to peak thrombin (min)	2	1160	89	0	-1.39 (-2.27--0.51)	*0.0020**
White Blood Count ($x10^9$/L)	4	2551	239	27.9	0.51 (-0.16-1.18)	*0.1374*
PRE-CHEMOTHERAPY						
D-dimer (ug/mL)[a]	4	404	48	0	2.30 (1.19-3.41)	*<0.0001**
Hemoglobin (g/L)	5	1034	161	0	**-0.77 (-3.70-2.17)**	*0.6095*

Mean Platelet Volume (fL)	2	678	50	0	-0.39 (-0.73--0.05)	*0.0226**
Platelet Count (x10^9/L)	5	1034	161	19.4	10.92 (-9.60-31.44)	*0.2968*
Soluble P-Selectin[c]	2	233	26	0	6.67 (-3.83-17.16)	*0.2131*
White Blood Count (x10^9/L)	4	923	120	0	**0.07 (-0.39-0.52)**	*0.7660*
PREOPERATIVE						
Activated Partial Thromboplastin Time (sec)	4	926	116	39.2	-0.73 (-2.34-0.89)	*0.3800*
Alanine transaminase (IU/L)	2	618	78	0	1.09 (-4.66-6.84)	*0.7105*
Albumin (g/L)	2	359	22	0	-1.53 (-3.60-0.54)	*0.1475*
C-Reactive Protein (mg/L)	3	390	32	0	-0.45 (-2.83-1.94)	*0.7134*
D-dimer (ug/mL)	4	534	77	21.4	0.13 (-0.16-0.42)	*0.3751*
Latex photometric immunoassay[d]	1	75	21	NA	0.30 (-0.37-0.97)	*0.3782*
Not stated	3	459	56	26.9	0.16 (-0.27-0.59)	*0.4673*
Fibrinogen (g/L)[e]	2	725	90	0	**0.24 (0.03-0.45)**	*0.0261**
Hemoglobin (g/L)	3	817	79	51.6	-7.05 (-15.99-1.89)	*0.1222*
Lymphocyte Count (x10^9/L)	3	1048	65	69.9	-0.43 (-0.88-0.03)	*0.0647*
Neutrophil Count (x10^9/L)	2	742	59	0	-0.15 (-0.91-0.61)	*0.6922*
Platelet Count (x10^9/L)	6	1880	181	49.2	**15.41 (-9.07-39.90)**	*0.2173*
Prothrombin time (sec)	2	233	17	0	**-0.20 (-0.76-0.36)**	*0.4802*
Prothrombin time (%)	2	618	78	0	-5.97 (-12.27-0.34)	*0.0635*
Thrombin time (sec)	2	725	90	0	0.00 (-0.30-0.30)	*1.0000*

White Blood Count (x10^9/L)	4	1540	138	5.4	0.05 (-0.45-0.55)	*0.8548*

*Statistically significant (*p<0.05)*

[a]D-dimer levels for the included studies were measured via quantitative latex-enhanced immunoturbidimetric immunoassay (cut-off for the assay: 0.5 ug/mL).

[b]Levels were measured using the Clauss method in one study whereas the method of measurement not stated in the other study

[c]Soluble P-selectin measured using human sP-selectin Immunoassay from R&D Systems Inc.

[d]D-dimer levels measured via latex photometric immunoassay (cut-off for the assay: 1.0 ug/mL).

[e]Method of measurement not stated.

Supplemental Table 11. Sensitivity analyses of the odds ratios (OR) for dichotomous biomarker cut-offs with VTE in cancer patients (excluding studies that screened for VTE)

Biomarkers	**Cut-off**	**N of studies**	**Sample size**	**VTE**	**I^2, %**	**Pooled OR**	***P-value***
AT CANCER DIAGNOSIS							
Hemoglobin (g/L)	<100	4	1576	252	0	1.86 (1.21-2.86)	*0.0048**
Neutrophil Lymphocyte Ratio	≥ 3	2	818	82	67.1	1.61 (0.55-4.74)	*0.3904*
Platelet Count ($x10^9$/L)	≥ 350	5	1695	268	57.9	1.09 (0.59-2.00)	*0.7797*
White Blood Count ($x10^9$/L)	>11	4	1025	164	2.2	1.67 (1.06-2.62)	*0.0272**
PRE-CHEMOTHERAPY							
Hemoglobin (g/L)	<100	10	7134	618	45.2	1.14 (0.76-1.71)	*0.5168*
Neutrophil Lymphocyte Ratio	≥ 3	2	1236	141	0	1.47 (1.01-2.13)	*0.0421**

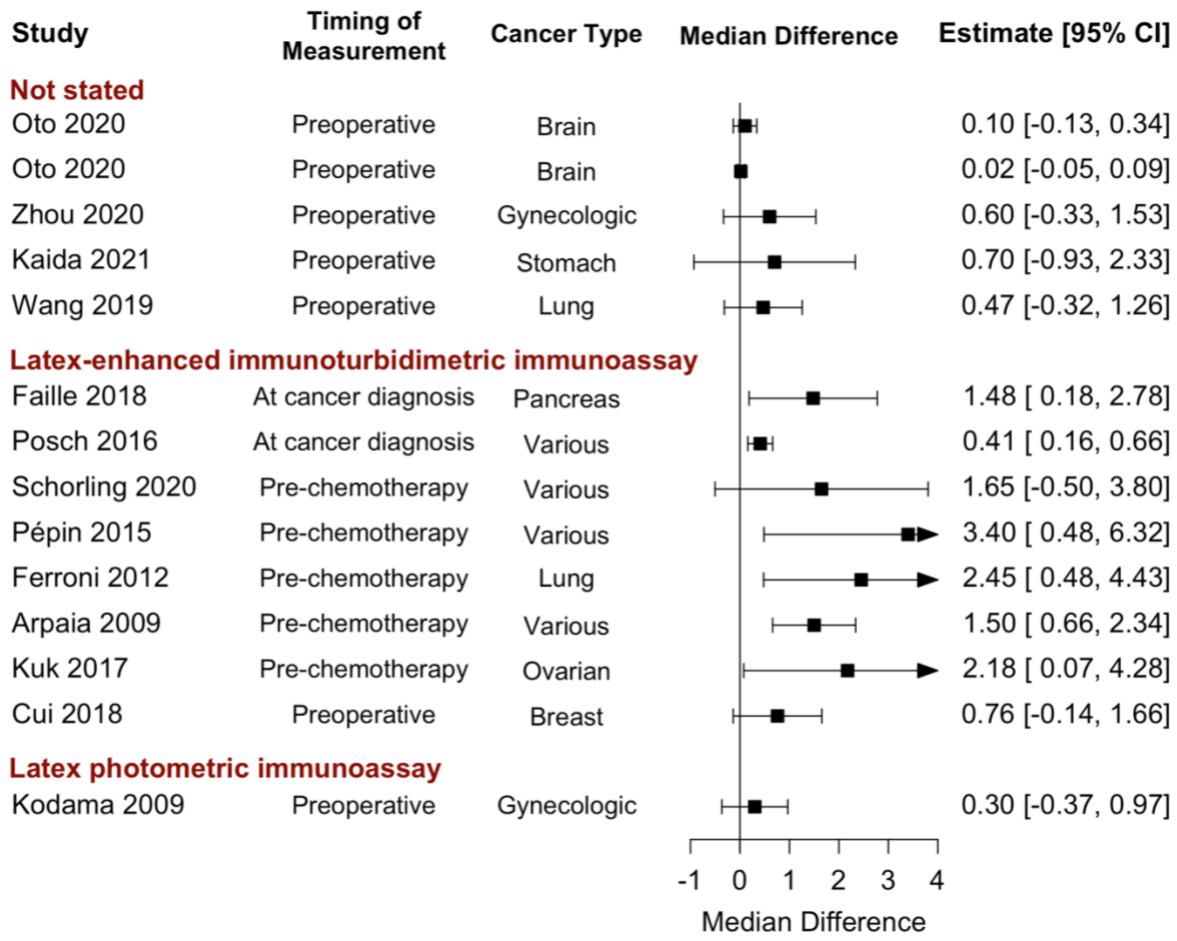
Platelet Count (x10^9/L)	≥ 350	8	6508	51 9	29.1	0.94 (0.69- 1.29)	*0.7190*
Platelet Lymphocyte Ratio	≥ 260	2	1236	14 1	22.1	1.36 (0.79- 2.35)	*0.2742*
White Blood Count (x10^9/L)	> 11	9	10911	63 5	55.1	1.20 (0.80- 1.78)	*0.3799*

*Statistically significant ($p<0.05$)

Supplemental Table 12. Sensitivity analyses of the odds ratios (OR) of VTE and blood parameters from the Khorana score in non-myeloma cancer patients

Biomarkers	**Cut-off**	**N of studies**	**Sample size**	**VTE**	**I^2, %**	**Pooled OR**	***P-value***
AT CANCER DIAGNOSIS							
Hemoglobin (g/L)	< 100	4	1576	252	0	1.86 (1.21-2.86)	*0.0048* *
Platelet Count (x10^9/L)	≥ 350	5	1695	268	57.9	1.09 (0.59-2.00)	*0.7797*
White Blood Count (x10^9/L)	> 11	4	1025	164	2.2	1.67 (1.06-2.62)	*0.0272* *
PRE-CHEMOTHERAPY							
Hemoglobin (g/L)	<100	8	4064	478	16.9	1.41 (0.95-2.10)	*0.0884*
Platelet Count (x10^9/L)	≥ 350	7	3638	391	37.2	0.96 (0.67-1.38)	*0.8435*
White Blood Count (x10^9/L)	> 11	8	8041	507	59.5	1.22 (0.78-1.91)	*0.3843*
PREOPERATIVE							
Hemoglobin (g/L)	< 100	2	800	73	28.3	0.99 (0.52-1.89)	*0.9816*

*Statistically significant ($p<0.05$)



Supplemental Figure 1. Forest plot of the median differences in d-dimer levels by type of assays between VTE and non-VTE cancer patients

Chapter 5

Association of baseline and longitudinal changes in inflammation and cardiac biomarkers with the risk of venous thromboembolism and clinically relevant bleeding in cancer patients

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Preface to Chapter 5

This Chapter presents another post-hoc analysis of the AVERT trial, conducted to investigate the association between select inflammatory and cardiac biomarkers and the risk of venous thromboembolism (VTE) and clinically relevant bleeding in patients with cancer. Cancer patients have an increased risk of both thrombotic and bleeding complications due to complex interactions between malignancy, its treatments and coagulation pathways. While biomarkers such as growth differentiation factor-15 (GDF-15), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and high-sensitivity troponin-T (hs-TnT) have shown prognostic value in other patient populations and settings, their role in predicting VTE and bleeding in patients with cancer remains uncertain. This Chapter explores their potential utility in risk prediction at baseline and additional timepoints following chemotherapy initiation.

5.1 Abstract

Background: Patients with cancer have an increased risk of venous thromboembolism (VTE) and bleeding. Inflammatory and cardiac biomarkers may predict these complications, but their role remains unclear.

Objectives: To examine associations between two inflammatory markers [C-Reactive Protein (CRP) and Growth Differentiation Factor-15 (GDF-15)] and two cardiac markers [N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity Troponin-T (hs-TnT)] with VTE and clinically relevant bleeding in cancer patients at intermediate to high risk of VTE (defined as Khorana score≥2).

Methods: We conducted a post-hoc analysis of the AVERT trial, which evaluated apixaban for VTE prevention in ambulatory cancer patients with Khorana score≥2. Biomarkers were measured at baseline and month-1, with CRP also measured at month-3. Fine and Gray regression models accounting for competing risk of death and, adjusted for age and advanced cancer, estimated subdistribution hazard ratios (SHR) for VTE and clinically relevant bleeding, adjusting for age, advanced cancer and accounting for the competing risk of death.

Results: Of 574 patients, 514 provided baseline samples. One- and three-month samples were available from 454 and 447, and 378 and 364, patients without prior VTE and bleeding events, respectively. Elevated baseline GDF-15 was associated with increased VTE risk [adjusted SHR:1.36 (95% CI:1.01-1.84); p=0.045]. NT-proBNP [adjusted SHR: 1.44 (95% CI:1.08-1.92); p=0.014] and CRP [adjusted SHR: 1.38 (95% CI: 1.07-1.76); p=0.012] were linked to bleeding risk. Increasing hs-TnT levels from baseline to month-1 was associated with higher VTE risk [adjusted SHR: 1.89 (95% CI:1.14-3.16); p=0.014]. Nomograms were developed to estimate VTE and clinically relevant bleeding risks.

Conclusions: Select inflammatory and cardiac markers were associated with VTE and bleeding risks in cancer patients with a Khorana score≥2 which can be determined using our nomograms. Prospective research is needed to confirm these findings.

Keywords: venous thromboembolism, bleeding, biomarkers, cancer inflammation

5.2 Introduction

Several risk factors and pathways contribute to a high risk of venous thromboembolism (VTE) in cancer patients. Concerning the etiology, evidence supports inflammation and coagulation as related and interacting processes. Briefly, inflammatory processes influence three key elements of coagulation including inflammation-induced coagulation activation, inflammation-induced downregulation of physiological anticoagulant pathways and inhibition of fibrinolysis.[1] Additionally, patients with DVT commonly present with cardinal signs of inflammation including heat, redness, pain and swelling. The association between inflammation and coagulation is further highlighted by the elevated risk of VTE in individuals with inflammatory diseases such as rheumatic arthritis[2], systemic lupus erythematosus[2,3], systemic sclerosis[2,4] and inflammatory bowel disease.[5,6] This connection between inflammation and coagulation has prompted several studies to evaluate the relationship between inflammatory biomarkers and VTE risk. In two systematic review and meta-analyses of population-based studies, higher levels of C-reactive protein (CRP), a well-known inflammatory biomarker, were associated with an increased risk of VTE.[7,8] Other studies have demonstrated a probable association between VTE and elevated levels of the inflammatory markers growth differentiation factor-15 (GDF-15) and interleukin-6 (IL-6), again supporting a relationship between inflammation and VTE risk.[9,10] However, the association between GDF-15 and VTE in cancer patients remains a matter of debate. In our previous studies evaluating the risk of VTE and bleeding in ambulatory cancer patients with high GDF-15 at 1-month after chemotherapy initiation, increased GDF-15 levels were associated with an increased risk of both VTE and bleeding risk.[11,12] However, in the prospective Vienna Cancer and Thrombosis Study (CATS) cohort, no relationship between GDF-15 and VTE was found, although elevated GDF-15 was linked to an increased risk of bleeding.[13,14]

Cardiac biomarkers such as natriuretic peptides and troponins have also been implicated in VTE risk. Elevated levels of n-terminal pro b-type natriuretic peptide (NT-ProBNP) and high-sensitivity troponin T (hs-TnT) have been associated with increased thrombotic risk in the general population.[15,16] NT-proBNP is a marker of myocardial stress and hs-TnT is a marker of myocardial damage.[17–19] Although the exact mechanism remains unclear, it is hypothesized that NT-proBNP and hs-TnT may reflect a prothrombotic state since they are typically elevated in a variety of cardiac conditions[15,17–19] which are known to provoke VTE such as heart failure and

peripheral atherosclerotic diseases.[20,21] Moreover, in atrial fibrillation patients, NT-proBNP and hs-TnT have been identified as independent predictors of stroke and systemic embolism, with hs-TnT also serving as a prognostic factor for major bleeding, further reflecting a potential relationship between coagulation and cardiac markers.[22–24] However, little is known about the relationship between cardiac biomarkers such as NT-proBNP, hs-TnT and VTE risk in cancer patients.

In patients with cancer, a proinflammatory and prothrombotic state is even more pronounced due to the malignancy itself and treatment. However, the relationship between inflammatory and cardiac markers and VTE among patients with cancer remains less clear. Two nested case-control studies of patients with cancer identified CRP as a potential predictor of VTE risk,[25,26] though a prospective cohort study of patients with cancer failed to demonstrate a significant association after multivariate adjustment.[27] Interestingly, a recent study exploring the early dynamics of CRP levels in patients treated with immune checkpoint inhibitors (ICI) reported that patients who experienced a CRP rise (defined as a ≥ two-fold increase in CRP levels from baseline) had a higher risk of developing VTE.[28]

To address these knowledge gaps, the aim of this study was to investigate the association between baseline levels of two inflammatory markers (CRP, GDF-15) and two cardiac markers (NT-proBNP, hs-TnT) with VTE in cancer patients. Additionally, following recommendations to assess longitudinal changes in biomarkers[29], we examined the relationship between longitudinal changes in GDF-15, CRP, NT-proBNP and hs-TnT and the occurrence of VTE. We also investigated the association between these biomarkers, both at baseline and longitudinally, with the risk of clinically relevant bleeding.

5.3 Methods

The Ottawa Health Science Network Research Ethics Board has reviewed and approved this study (20240294-01H).

Study Design

This is a post-hoc analysis of the AVERT trial (Apixaban to Prevent VTE in Patients with Cancer), evaluating the association between baseline and longitudinal biomarker levels for the prediction of cancer-associated VTE and bleeding. The AVERT trial was a randomized, double-

blind placebo-controlled trial assessing the efficacy and safety of apixaban compared to placebo in preventing VTE in ambulatory cancer patients with intermediate to high risk of VTE (defined as a Khorana score ≥ 2) between February 2014 to April 2018 from 13 Canadian hospitals. Patients were randomized 1:1 to apixaban 2.5 mg twice daily vs placebo for 6 months. Full details on the methodology and eligibility for the trial have been published.[30]

Participants

The AVERT trial enrolled ambulatory cancer patients, aged 18 years or older, with newly diagnosed or progressive cancer and a Khorana score of 2 or more. Eligible patients were initiating a new course of chemotherapy and provided written informed consent. At the time of inclusion, participants were also asked for consent to store blood samples for future secondary research use. In this study, we included all patients enrolled in the AVERT trial who consented for additional blood draw for research. Patients with missing blood samples at baseline or during follow-up were excluded.

Variables and Outcomes

Patient demographics and characteristics, including ethnicity, age, cancer type, cancer stage (defined as advanced if the patient had hematological cancer or stage 3 or 4 solid cancer), sex (male or female as assigned at birth) and treatment group (i.e., apixaban vs placebo), were collected at the time of randomization. For this study, the primary outcome was occurrence of VTE, defined as objectively confirmed symptomatic or incidentally detected thromboembolic events, including proximal or distal lower or upper limb deep vein thrombosis (DVT), pulmonary embolism (PE), splanchnic or cerebral vein thrombosis occurring within the 7-months following enrollment. The secondary outcome was the composite of major bleeding and clinically relevant nonmajor bleeding (CRNMB) (both defined using the International Society on Thrombosis and Haemostasis definitions)[31,32], otherwise known as clinically relevant bleeding. These outcomes differ from the original trial, which focused on proximal DVT, PE and bleeding events within a 6-month follow-up period. All outcomes were adjudicated by a blinded outcome adjudication committee.

During the AVERT trial, blood samples were collected at baseline and at months 1, 3, 6 and 7 following enrollment. In this study, we analyzed blood samples and focused on biomarkers

measured at baseline, month-1 and month-3. Particularly, we measured GDF-15, NT-proBNP, hs-TnT and CRP levels at baseline, and CRP levels at month-1 and month-3. In addition, we included previously measured biomarkers at month-1 including GDF-15, NT-proBNP and hs-TnT levels which were part of previous research.[11] CRP was the only biomarker tested at month-3 given previous evidence suggesting an association between CRP changes in the first 3-months and VTE risk in cancer patients initiating immune checkpoint inhibitor therapy.[28] Due to funding and project constraints, the biomarkers were measured at three different labs. CRP was measured using particle-enhanced immunoturbidimetric assays on Roche cobas 6000 automated chemistry analyzer (at baseline) or Roche c702 instrument (month-1 and -3). GDF-15 was measured using an ELISA immunoassay (Biotechne Quantikine GDF-15, R&D systems) on Roche cobas 6000 automated chemistry analyzer (baseline) and an electrochemiluminescence immunoassay (Roche Elecsys assay, Roche Diagnostics) on Cobas e411 platform (month-1). NT-proBNP and hs-TnT were measured using electrochemiluminescence immunoassays on Roche cobas 6000 automated chemistry analyzer (baseline) or Roche Cobas e411 platform (Roche Diagnostics, Manheim, Germany) (month-1).

Statistical Analysis

We assessed patient characteristics and biomarker levels between patients with and without VTE and clinically relevant bleeding using descriptive statistics. Since all biomarker levels were right skewed, we reported biomarker levels as medians and interquartile ranges. Prior to imputation and regression analyses, biomarkers were log transformed and standardized by subtracting the mean and dividing by the standard deviation (SD). Then, patients with partial missing biomarker data were included and missing biomarker levels were imputed using single imputation predictive mean matching.

To assess the association between the biomarkers and clinical outcomes, we used Cox proportional hazard and Fine and Gray competing risk regression models. The Cox regression models were used to detect departures from linearity for continuous biomarkers. Specifically, to examine potential non-linear relationships between biomarkers and outcomes, we compared the Akaike Information Criterion (AIC) of restricted cubic spline cox regression models with 4-knots and 3-knots with the AIC of a linear model. The model with the smallest AIC was considered as having the best fit. We also plotted the restricted cubic spline models with 4-knots to visually

assess for non-linearity. To verify proportionality over time, scaled Schoenfeld residuals were plotted over time and visually inspected for non-proportionality. In cases where biomarkers showed evidence of non-linear associations with outcomes, we plotted the hazard ratio across different biomarker levels. For biomarkers demonstrating a linear relationship with VTE or clinically relevant bleeding, we used Fine and Gray competing risk regression models, incorporating linear terms and adjusting for the competing risk of all-cause mortality. To confirm the proportional subdistribution hazards assumption was met, we plotted the cumulative incidence functions and visually inspected for consistent, non-crossing separation between the groups

We performed separate regression analyses to evaluate the impact of baseline biomarker levels and changes in biomarkers over time (from baseline to month-1 or month-3) on the risk of future VTE and clinically relevant bleeding. To assess the baseline association, only the transformed and standardized baseline biomarker values were included in the model. For changes over time, we included the relative differences in log biomarker levels (i.e., log month-1 or log month-3 values minus log baseline) while adjusting for the log baseline value. Multivariate models were used to account for potential confounders (i.e., age and metastatic/advanced cancer). To help with clinical applicability, we generated nomograms to help describe the association between the biomarkers and outcomes. Sensitivity analyses were performed to assess the robustness of results, one analysis without imputations and the other by intervention group (i.e., apixaban vs placebo). We evaluated biomarkers for predicting VTE in the placebo group and clinically relevant bleeding in the apixaban group, as these populations were considered higher risk for these outcomes. For comparison, we also analyzed the risk of VTE and clinically relevant bleeding in previously defined CRP change subgroups including CRP rise (defined as a two-fold or greater increase in CRP levels from baseline) and CRP decline (defined as a 50% or greater decrease in CRP levels from baseline)[28] using the values from month-1 and month-3. For all analyses, a p-value below 0.05 was considered statistically significant and, all analyses were performed in SAS version 9.4 (SAS Institute, Inc) or R Studio (R Core Team (2024), Vienna, Austria).

5.4 Results

Of 574 patients enrolled in the AVERT trial between February 2014 and April 2018, a total of 514 patients consented to providing blood samples at baseline (Figure 1). Of these, 43 patients developed VTE (24 DVT, 15 PE, 2 combined DVT and PE, 2 splanchnic vein thrombosis) and 46 developed clinically relevant bleeding events (11 major bleeding and 35 clinically-relevant non-major bleeding events) during the 7-month follow-up. To analyze the change in biomarker levels from baseline to month-1, we excluded patients who did not consent to providing 1-month blood samples as well as those who died or developed an event prior to the month-1 follow-up visit (Figure 1). Similarly, to analyze the change in CRP levels from baseline to month-3, we also excluded patients who did not provide consent, and those with previous events or deaths (Figure 1). At baseline, 28 GDF-15, 31 NT-proBNP, 56 hs-TnT, and 17 CRP values were imputed. At month-1, 12 GDF-15, 12 NT-proBNP, 8 hs-TnT, and 6 CRP values required imputation. At month-3, no values were imputed.

Overall, for the 514 patients included at baseline, the mean (SD) age at enrollment was 62 (12.1) and the median follow-up was 196 days. The most common primary cancer sites were gynecologic (n=138), lymphoma (n=131) and pancreatic (n=67). Among the patients, 41.8% were male and 50.2% patients were randomized to receive apixaban. Consistent with the main findings of the AVERT trial, the incidence of VTE was higher among patients randomized to placebo than those randomized to apixaban (69.8% vs 30.2% Table 1). The mean (SD) biomarker levels stratified by VTE and clinically relevant bleeding are presented in Table 1 and Supplemental Table 1, respectively.

At baseline, there was no evidence of non-linear associations between any of the four biomarkers and outcomes. Therefore, we used Fine and Gray competing risk regression with linear terms to determine the association between baseline biomarkers and future risk of VTE and clinically relevant bleeding, with death as a competing risk (Table 2 and 3). The results suggest that elevated baseline GDF-15 was significantly associated with an increased risk of VTE [SHR: 1.36 (95% CI: 1.01-1.84), p=0.045], but not bleeding, after adjustment for age and advanced cancer (Table 3). Biomarkers which were not significantly associated with an increased risk of VTE but were associated with a significantly increased risk of clinically relevant bleeding included NT-proBNP and CRP [SHR: 1.44 (1.08-1.92), p=0.014; SHR per 1 SD log increase: 1.38 (1.07-1.76), p=0.012, respectively] (Table 3) after multivariate adjustment.

In our sensitivity analyses excluding imputed data and focusing on patients randomized to placebo or apixaban, similar effect measures were reported (Supplementary Tables 2 - 4).

In our analyses of changes over time, we again found no evidence of non-linear associations, permitting us to fit Fine and Gray competing risk regression models without restricted cubic splines. According to our multivariate analyses, increasing hs-TnT levels from baseline to month-1 (i.e., log hs-TnT at month-1 minus log hs-TnT at baseline) was significantly associated with an increased risk of VTE [SHR: 1.89 (95% CI: 1.14-3.16), p=0.014] but not bleeding (Table 3). This association remained significant in sensitivity analyses without imputations and in patients receiving placebo (Supplementary Table 2 and 3). Although we did not perform multivariate analyses given the lower number of events and sample size, an increase in CRP levels from baseline to month-3 was also significantly associated with VTE risk [SHR: 1.89 [95% CI: 1.14-3.16), p =0.014] in the univariate model but not with bleeding (Table 2). When CRP was analyzed categorically in subgroups of CRP change (i.e., CRP rise and CRP decline)[28], patients with a CRP decline of 50% or greater in the first three months had a significantly lower risk of VTE compared to those without [SHR: 0.34 (95% CI: 0.12-0.96), p=0.042] which was no longer significant after multivariate adjustment [SHR: 0.33 (95% CI: 0.11-1.02), p=0.054). Additionally, our analyses revealed that increasing NT-proBNP levels from baseline to month-1 was significantly associated with an increased risk of clinically relevant bleeding [SHR: 1.41 (95% CI: 1.04-1.91), p =0.027; Table 3]. However, a high effect measure was also reported in relation to VTE and, in our analysis of patients randomized to apixaban, a diminished effect measure was observed.

Four nomograms were generated based on the results of our biomarker analyses – one for predicting the risk of VTE using baseline GDF-15, one for predicting the risk of clinically relevant bleeding using baseline biomarkers (i.e., CRP and NT-proBNP), one for predicting the risk of VTE using changes in hs-TnT levels from baseline to month-1 and one for predicting the risk of clinically relevant bleeding using changes in NT-proBNP levels from baseline to month-1 (Figure 2-3). In all four nomograms, the number of assigned points and predicted risk of outcome increased with increasing levels of biomarkers. To illustrate how these nomograms work, we consider a hypothetical example for predicting the risk of clinically relevant bleeding using baseline biomarkers (Figure 2). If a patient has a natural log CRP of 1 (equivalent to 2.7 mg/dL) and a natural log NT-proBNP of 7 (equivalent to 1100 pg/mL), they would be assigned

50 and 40 points, respectively, based on the top point axis. The sum of these values would then be used to generate a predicted risk probability using the bottom point axis. In this example, the patient would have a total of 90 points which would correspond to an estimated 15% risk of clinically relevant bleeding.

5.5 Discussion

In this post-hoc analysis of the AVERT trial, higher baseline GDF-15 was associated with an increased risk of VTE but not bleeding, meanwhile, higher baseline CRP and NT-proBNP levels were associated with an increased risk of clinically relevant bleeding, but not VTE, during 7-months of follow-up after chemotherapy initiation. Our results also suggested that an increase in hs-TnT levels from baseline to month-1 and an increase in CRP levels from baseline to month-3 were associated with an increased 7-month risk of VTE, but not bleeding. Lastly, we found that increasing NT-proBNP levels from baseline to month-1 was associated with an increased risk of clinically relevant bleeding, though this association was no longer significant in patients randomized to the apixaban group. Based on these results, four nomograms were generated for the prediction of VTE and clinically relevant bleeding in patients with cancer.

Our findings suggest that, at baseline, biomarkers such as GDF-15, CRP and NT-proBNP may help optimize risk assessment for VTE or clinically relevant bleeding in patients with cancer starting chemotherapy, potentially facilitating decision-making regarding primary thromboprophylaxis. In particular, GDF-15, an inflammatory biomarker, showed potential as baseline predictor for VTE with no link to bleeding, though this contrasts with results from the Vienna CATS studies, which reported a relationship between GDF-15 and bleeding risk with no link to VTE.[13,14] The differences in study patient populations and follow-up durations between the AVERT trial and Vienna CATS cohort may explain these inconsistencies. Particularly, the AVERT trial included patients at intermediate to high risk of VTE (Khorana score≥2) with almost half of the patients randomized to receive apixaban as primary thromboprophylaxis and followed for 7-months whereas, the VIENNA CATS cohort included a broader cancer population which were followed up to 24 months and prophylactic anticoagulation was not routinely given in their cohort. Thus, other studies are needed to determine the role of baseline GDF-15 in cancer patients.

Additionally, in our study, we found an association between CRP, another inflammatory biomarker, was associated with an increased risk of clinically relevant bleeding. Although GDF-15 and CRP are both inflammatory biomarkers, they have different properties, which may explain why one is associated with VTE while the other is associated bleeding. GDF-15 is a stress-response cytokine expressed in response to inflammation, oxidative stress, hypoxia, telomere erosion and oncogene activation[33] whereas, CRP is an acute phase reactant protein expressed primarily in response to infection and inflammation.[34] GDF-15 is thus known to have a broader role in inflammatory or stress responses compared to CRP. A possible mechanism linking GDF-15 to VTE is via the activation of Smad2/psmad2/snail pathway by GDF-15 expression which promotes endothelial-to-mesenchymal transition and reduces their antithrombotic ability.[35] The mechanistic link between CRP and bleeding is not fully understood, but CRP could be an indicator of other comorbidities associated with increased risk of bleeding such as atrial fibrillation[36], hypertension[37] or chronic kidney disease.[38]

Baseline NT-proBNP was also identified as another predictor for clinically relevant bleeding. NT-proBNP is a cardiac marker secreted in response to myocyte stretch, hypoxia and endocrine activation.[17,39] While it is a biomarker of cardiac stress primarily used to monitor heart failure patients,[40] our findings suggest that NT-proBNP may also be useful in cancer patients initiating chemotherapy to predict clinically relevant bleeding. The potential link between NT-proBNP and bleeding could be related to the physiological effects of its biologically active counterpart, B-type natriuretic peptide (BNP), which inhibits the renin-angiotensin system and the sympathetic nervous system[17], potentially influencing fibrinolysis and hemostasis. Moreover, elevated NT-proBNP has been linked to several bleeding risk factors including low hemoglobin,[41,42] hypertension,[43] metastatic disease,[44] systematic inflammation[45] and chronic kidney disease,[46,47] which could also explain the increased susceptibility to bleeding in patients with elevated NT-proBNP levels.

Beyond baseline measures, longitudinal changes in biomarkers can provide insights into changes in risk during treatment (i.e., chemotherapy or anticoagulation therapy). Our findings suggest that increasing hs-TnT levels from baseline to month-1 and CRP levels from baseline to month-3 are associated with higher VTE risk. Elevated 1-month hs-TnT (>14 pg/mL) was previously identified as predicting future VTE events,[11] and our study extends this by demonstrating that increases in hs-TnT levels from baseline to month-1 may serve as an indicator

of increased VTE risk after initiating chemotherapy. Since hs-TnT is a marker of myocardial damage, rising hs-TnT may be related to the damaging effects of chemotherapy on the cardiovascular system, a condition known as chemotherapy-related cardiotoxicity, which is presumed to impair circulation and predispose to thrombosis.[48]

Additionally, the positive association between CRP changes at 3-months and VTE aligns with previous research. A study by Moik et al[28] found that an early CRP rise (defined as a two-fold or greater increase in CRP levels in the first 3-months from baseline) was associated with increased VTE risk in cancer patients treated with immune checkpoint inhibitors.[28] Since our study included cancer patients initiating any chemotherapy (not limited to immune checkpoint inhibitors), our findings suggest that this relationship may also extend to this patient population, though confirmation in larger studies are needed due to our small sample size and low number of events. However, in a study of patients with metastatic colorectal cancer, patients who developed thrombosis tended to have increasing high-sensitivity CRP levels during the course of treatment after 2 months of chemotherapy,[49] aligning with our results. Thus, there may be an inflammatory response occurring during the first few months of chemotherapy, increasing the likelihood of thrombosis. The lack of 1-month CRP-VTE association in our study raises the possibility that a shorter follow-up period may not be sufficient to capture the inflammatory effects of chemotherapy, supporting future research on CRP changes at 2 to 3 months.

Finally, increasing NT-proBNP levels from baseline to month-1 was associated with increased clinically relevant bleeding risk, but an elevated hazard ratio was observed for VTE contraindicating its use as a potential bleeding predictor. Additionally, in patients randomized to apixaban, a diminished effect measure was reported, suggesting that it may not be a useful predictor for clinically relevant bleeding complications in patients on anticoagulation. The reduced effect measure in apixaban patients could be due the pleiotropic effects of direct oral anticoagulants (DOACs), which according to Mele et al[50], may lower NT-proBNP through their anti-inflammatory and endothelial modulating actions. Therefore, NT-proBNP may not be a useful longitudinal biomarker to use for monitoring changes in risk of bleeding in cancer patients on DOACs.

The current study has multiple clinical implications. For one, this study highlights the role of two inflammatory and two cardiac markers for assessing, as well as monitoring, the risks of VTE and clinically relevant bleeding in patients with cancer starting chemotherapy. The

associations identified in this study could help to further refine risk assessment models such as the Khorana score to guide decisions about thromboprophylaxis. Although these biomarkers are not routinely measured, some guidelines recommend assessing some of these biomarkers for other cancer-related outcomes including cardiotoxicity and cancer-related fatigue.[51–53] Therefore, these biomarkers may increasingly become part of routine clinical practice, especially with the rapid advancements in technology. Moreover, in this study, we generated four nomograms to predict individual risk of VTE and clinically relevant bleeding based on the significant biomarkers identified in this study. These nomograms may help to better stratify patients' risk, tailor treatment strategies, and monitor responses to therapy more effectively. As these nomograms are refined and validated, they could potentially become a helpful tool to make decisions about thromboprophylaxis and bleeding management, leading to improved patient outcomes.

Our study has limitations that should be considered. First, although we found significant associations between select biomarkers and future VTE or bleeding risks, we cannot definitively establish causality. Second, the modest sample size and number of events limited our ability to control for all potential confounders, therefore residual confounding may be present. Particularly, some biomarkers may be influenced by comorbidities or therapies (e.g., surgery, radiation therapy) common in cancer patients. However, we adjusted for age and advanced cancer diagnosis since these are well-known time-invariant risk factors for biomarker variability and VTE and bleeding risk. Third, the AVERT trial included only selected cancer patients with intermediate-high VTE risk initiating chemotherapy defined by Khorana score≥2. Additionally, some cancer types were excluded so the results may not be generalizable to all cancer types (e.g., acute leukemia and myeloproliferative neoplasms). Similarly, since the biomarkers were measured at baseline, month-1 and month-3 after initiating chemotherapy, the predictive ability of the biomarkers may not extend to other timepoints and in cancer patients initiating other therapies. Investigating a different length of follow-up may be of interest to other researchers, however, most VTE events occur within the first six months after diagnosis[54] and most clinically relevant bleeding events likely occur while on anticoagulation. It is also important to note that the biomarkers, at different timepoints, were measured in different labs which may have led to variations in biomarker values. Lastly, this study does not address the practicality and cost-effectiveness of implementing the use of these biomarkers in clinical practice.

In conclusion, our study showed that elevated baseline GDF-15 was associated with increased VTE risk, while elevated baseline NT-proBNP and CRP levels were associated with a higher clinically relevant bleeding risk in cancer patients with a Khorana score≥2. Changes in hs-TnT and CRP over time could also predict VTE risk. Four nomograms were generated based on these findings, which may serve as a valuable tool for risk assessment and monitoring. Further large prospective studies are needed to confirm our findings and the clinical utility of these biomarkers.

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Table 1. Baseline characteristics and laboratory results of cancer patients with and without venous thromboembolism (VTE)

	VTE (n=43)	No VTE (n=471)
Age (years), mean (SD)	64.0 (11.1)	62.0 (12.1)
Male sex, n (%)	20 (46.5)	195 (41.4)
BMI (kg/m^2), mean (SD)	27.5 (25.1-32.0)	27.7 (23.7-35.1)
Previous VTE, n (%)	3 (7.0)	13 (2.8)
Randomized to apixaban, n (%)	13 (30.2)	245 (52.0)
Randomized to placebo, n (%)	30 (69.8)	226 (48.0)
Antiplatelet use, n (%)	7 (16.3)	100 (21.2)
Known metastatic or advanced cancer, n (%)	35 (81.4)	418 (88.8)
Primary cancer site, n (%)		
Brain	3 (7.0)	19 (4.0)
Breast	0	17 (3.6)
Gastrointestinal	9 (20.9)	50 (10.6)
Gynecologic	8 (18.6)	130 (27.6)
Hematological	0	17 (3.6)
Lung	0	51 (10.8)
Lymphoma	8 (18.6)	123 (26.1)
Pancreas	12 (27.9)	55 (11.7)
Other	3 (7.0)	9 (1.9)
Laboratory test results at baseline, mean (SD)		
log(GDF-15, pg/mL)	7.3 (0.7)	7.1 (0.7)
log(NT-proBNP, pg/mL)	4.8 (1.0)	4.9 (1.0)
log(hs-TnT, pg/mL)	2.2 (0.7)	2.1 (0.5)
log(CRP, mg/dL)	0.2 (1.4)	0.01 (1.3)

Laboratory test results at month-1, mean (SD)*		
log(GDF-15, pg/mL)	8.0 (0.8)	7.6 (0.8)
log(NT-proBNP, pg/mL)	5.1 (1.0)	4.7 (1.3)
log(hs-TnT, pg/mL)	2.3 (0.8)	1.9 (1.0)
log(CRP, mg/dL)	-0.7 (1.5)	-0.9 (1.4)
Laboratory test results at month-3, mean (SD)*		
log(CRP, mg/dL)	-0.2 (1.5)	-1.2 (1.4)

Abbreviations: body mass index (BMI), c-reactive protein (CRP), growth-differentiation factor-15 (GDF-15), N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin-T (hs-TnT), standard deviation (SD), venous thromboembolism (VTE)

*At month-1, 30 patients had VTE and 424 patients had no VTE and at month-3, 16 patients had VTE and 362 patients had no VTE.

Table 2. Unadjusted association between biomarkers and risk of venous thromboembolism (VTE) and clinically relevant bleeding in cancer patients from the AVERT trial

Predictor[a]	**VTE**			**Clinically Relevant Bleeding**		
	N of events	**SHR (95% CI)**[d]	***p-value***	**N of events**	**SHR (95% CI)**[d]	***p-value***
GDF-15						
Baseline	43	1.30 (0.98-1.73)	*0.068*	46	1.10 (0.80-1.51)	*0.58*
Change from baseline to month-1[b]	30	1.27 (0.96-1.68)	*0.089*	30	1.21 (0.78-1.89)	*0.39*
NT-ProBNP						
Baseline	43	0.96 (0.72-1.29)	*0.80*	46	1.40 (1.06-1.85)	*0.017*
Change from baseline to month-1[b]	30	1.34 (0.95-1.90)	*0.093*	30	1.39 (1.02-1.89)	*0.036*
hs-TnT						
Baseline	43	1.22 (0.90-1.66)	*0.20*	46	0.98 (0.72-1.32)	*0.88*
Change from baseline to month-1[b]	30	1.91 (1.17-3.11)	*0.010*	30	1.17 (0.72-1.91)	*0.52*
CRP						
Baseline	43	1.14 (0.86-1.52)	*0.37*	46	1.44 (1.13-1.83)	*0.004*
Change from baseline to month-1[b]	30	1.16 (0.77-1.74)	*0.47*	30	1.12 (0.71-1.77)	*0.63*
Change from baseline to month-3[c]	14	1.88 (1.09-3.24)	*0.023*	16	0.62 (0.32-1.21)	*0.16*

[a] all baseline, month-1 and month-3 predictors were log transformed

[b] adjusted for baseline values

[c] adjusted for baseline values and change from baseline to month-1

[d] Per 1-unit standard deviation increase

Table 3. Adjusted association between biomarkers and risk of venous thromboembolism (VTE) and clinically relevant bleeding in cancer patients from the AVERT trial (adjusted for age and advanced/metastatic cancer)

Predictor[a]	**VTE**			**Clinically Relevant Bleeding**		
	N of events	**SHR (95% CI)**[d]	***p-value***	**N of events**	**SHR (95% CI)**[d]	***p-value***
GDF-15						
Baseline	43	1.36 (1.01-1.84)	*0.045*	46	1.09 (0.78-1.51)	*0.62*
Change from baseline to month-1[b]	30	1.27 (0.95-1.68)	*0.10*	30	1.23 (0.79-1.91)	*0.37*
NT-ProBNP						
Baseline	43	0.94 (0.70-1.27)	*0.70*	46	1.44 (1.08-1.92)	*0.014*
Change from baseline to month-1[b]	30	1.30 (0.89-1.89)	*0.18*	30	1.41 (1.04-1.91)	*0.027*
hs-TnT						
Baseline	43	1.22 (0.88-1.69)	*0.23*	46	0.98 (0.71-1.36)	*0.92*
Change from baseline to month-1[b]	30	1.89 (1.14-3.16)	*0.014*	30	1.15 (0.76-1.74)	*0.51*
CRP						
Baseline	43	1.22 (0.91-1.64)	*0.18*	46	1.38 (1.07-1.76)	*0.012*
Change from baseline to month-1[b]	30	1.12 (0.74-1.69)	*0.58*	30	1.13 (0.72-1.78)	*0.60*

[a] all baseline, month-1 and month-3 predictors were log transformed

[b] adjusted for baseline values

[c] adjusted for baseline values and change from baseline to month-1

[d] Per 1-unit standard deviation increase

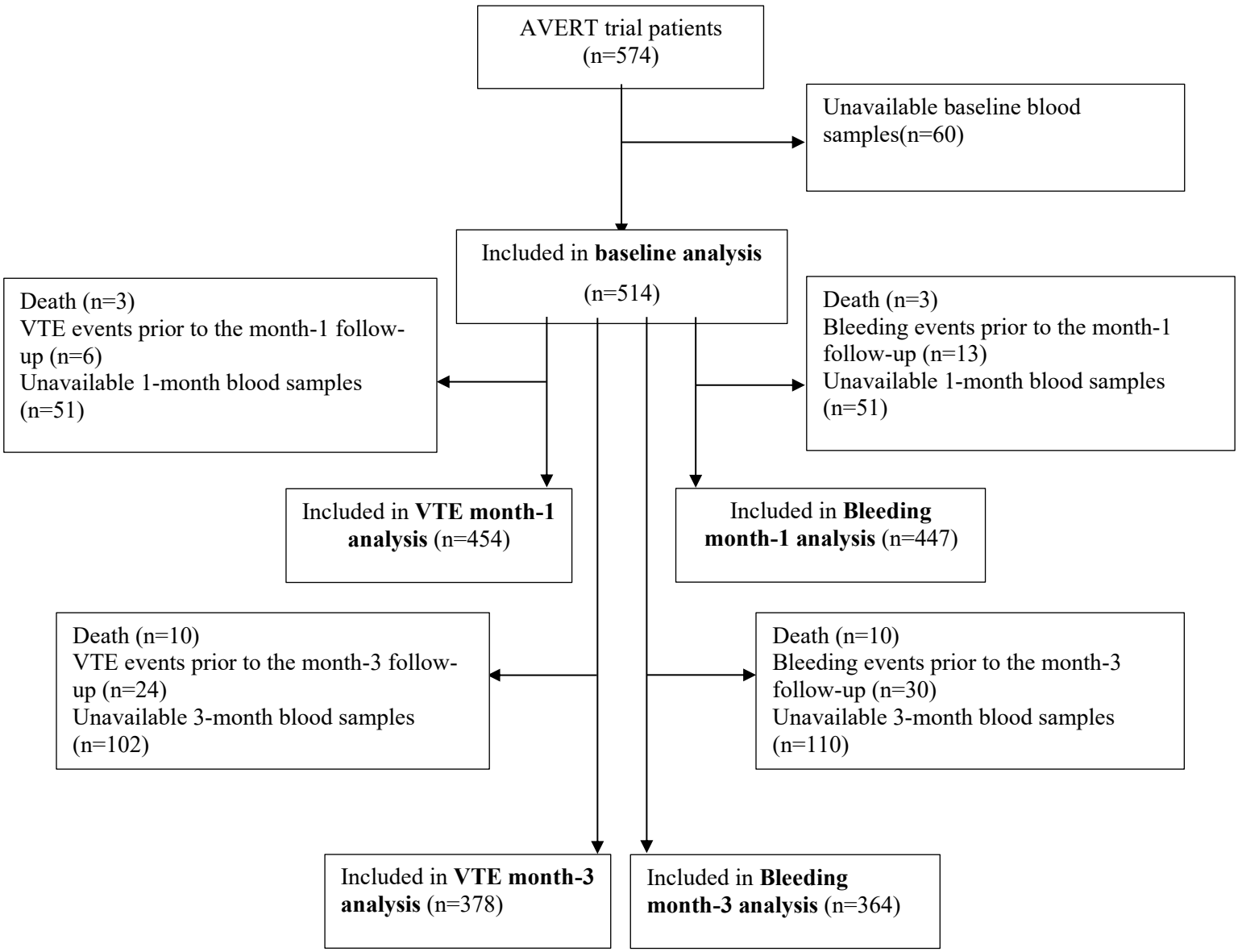

Figure 1. Flow diagram of patients included in the different venous thromboembolism (VTE) and clinically relevant bleeding analyses

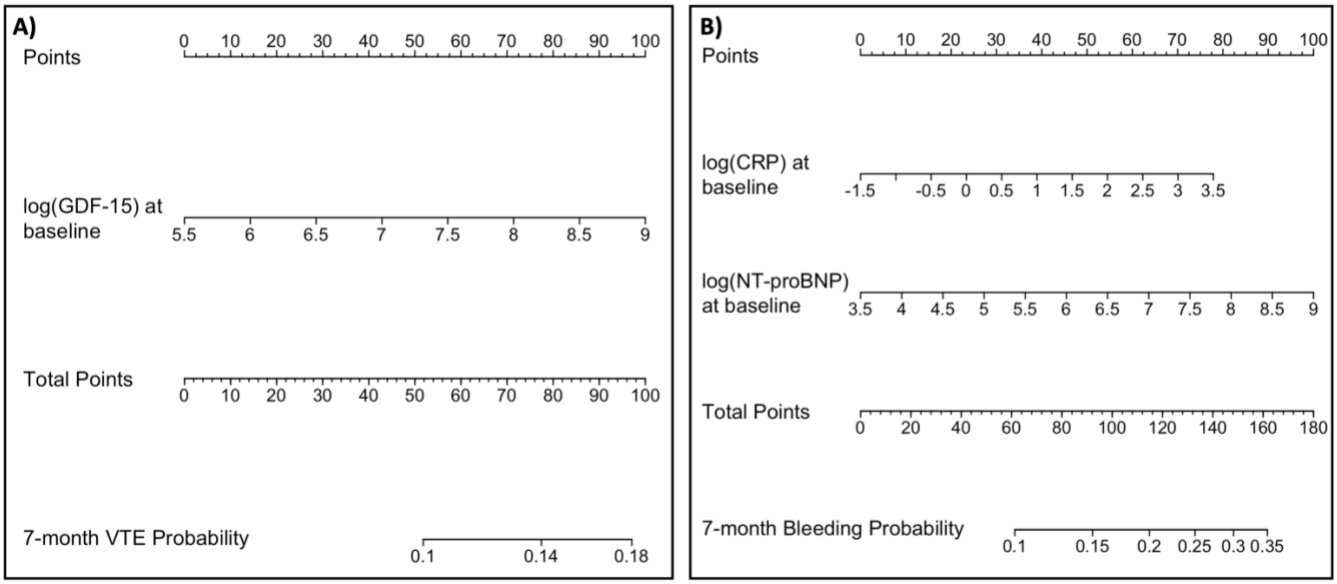

Figure 2. Nomograms for predicting the risk of a) venous thromboembolism (VTE) and b) clinically relevant bleeding using baseline biomarkers

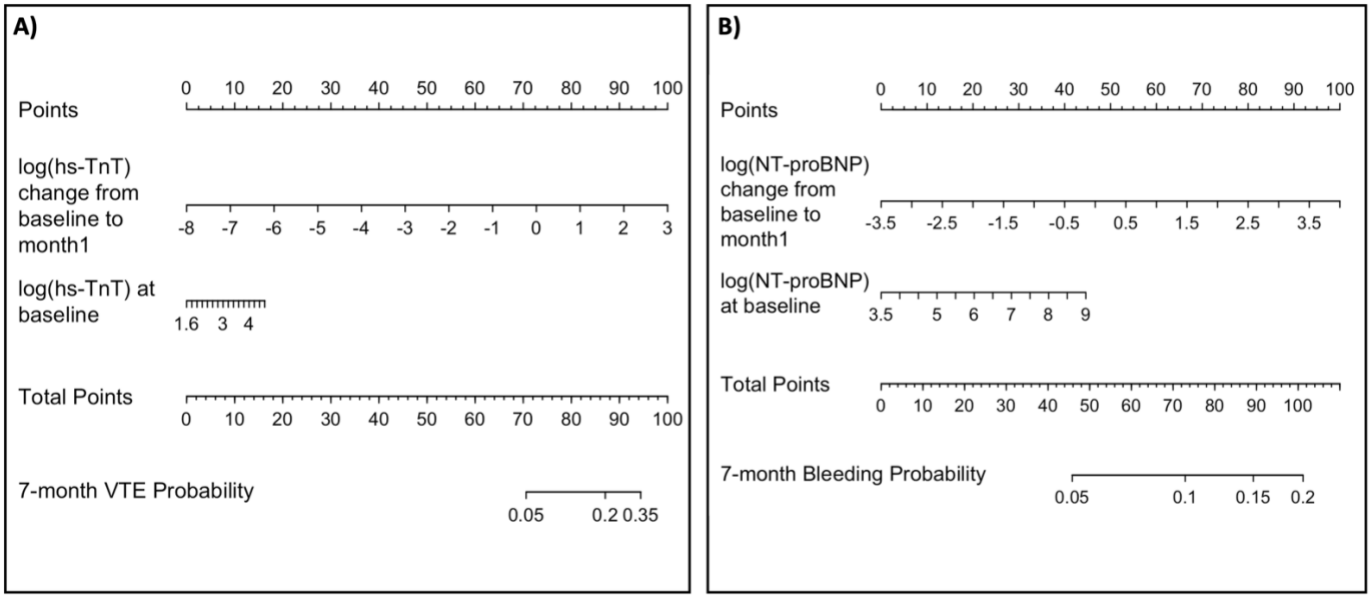

Figure 3. Nomograms for predicting the risk of a) venous thromboembolism (VTE) and b) clinically relevant bleeding using biomarker levels at baseline and month-1

5.7 Appendix

Supplemental Table 1. Baseline characteristics and laboratory results of cancer patients with and without bleeding

	Clinically Relevant Bleed (n=46)	**No Bleed (n=468)**
Age (years), mean (SD)	62.5 (14.7)	62.0 (11.8)
Male sex, n (%)	15 (32.6)	200 (47.7)
BMI (kg/m^2), mean (SD)	27.7 (23.9-33.5)	27.7 (23.7-35.1)
Previous VTE, n (%)	2 (4.4)	14 (3.0)
Randomized to apixaban, n (%)	30 (65.2)	228 (48.7)
Randomized to placebo, n (%)	16 (34.8)	240 (51.3)
Antiplatelet use, n (%)	10 (21.7)	97 (20.7)
Known metastatic or advanced cancer, n (%)	44 (95.7)	409 (87.4)
Primary cancer site, n (%)		
Brain	1 (2.2)	21 (4.5)
Breast	1 (2.2)	16 (3.4)
Gastrointestinal	5 (10.9)	54 (11.5)
Gynecologic	17 (37.0)	121 (25.9)
Hematological	1 (2.2)	16 (3.4)
Lung	2 (4.3)	49 (10.5)
Lymphoma	12 (26.1)	119 (25.4)
Pancreas	6 (13.0)	61 (13.0)
Other	1 (2.2)	11 (2.4)
Laboratory test results at baseline, mean (SD)		
log(GDF-15, pg/mL)	7.1 (0.8)	7.1 (0.7)

log(NT-proBNP, pg/mL)	5.2 (1.2)	4.8 (1.0)
log(hs-TnT, pg/mL)	2.1 (0.5)	2.2 (0.5)
log(CRP, mg/dL)	0.5 (1.3)	-0.02 (1.3)
Laboratory test results at month-1, mean (SD)*		
log(GDF-15, pg/mL)	7.8 (1.0)	7.6 (0.8)
log(NT-proBNP, pg/mL)	5.1 (1.1)	4.7 (1.3)
log(hs-TnT, pg/mL)	1.9 (0.8)	1.9 (1.0)
log(CRP, mg/dL)	-0.6 (1.6)	-0.9 (1.4)
Laboratory test results at month-3, mean (SD)*		
log(CRP, mg/dL)	-1.6 (1.5)	-1.1 (1.4)

***At month-1, 29 patients had VTE and 425 patients had no VTE and at month-3, 15 patients had VTE and 363 patients had no VTE.**

Supplemental Table 2. Sensitivity analysis without imputation (adjusted for age and advanced/metastatic cancer)

Predictor[a]	**N**	**VTE**			**N**	**Clinically Relevant Bleeding**		
		N of VTE	**SHR (95% CI)**[d]	***p-value***		**N of events**	**SHR (95% CI)**[d]	***p-value***
GDF-15								
Baseline	445	35	1.46 (1.05-2.04)	*0.026*	445	39	1.08 (0.75-1.54)	*0.69*
Change from baseline to month 1[b]	393	25	1.36 (0.99-1.87)	*0.055*	387	26	1.38 (0.90-2.12)	*0.14*
NT-ProBNP								
Baseline	442	33	1.04 (0.74-1.47)	*0.81*	442	39	1.43 (1.02-2.00)	*0.037*
Change from baseline to month-1[b]	391	23	1.60 (0.98-2.61)	*0.060*	385	25	1.64 (1.13-2.38)	*0.009*
hs-TnT								
Baseline	419	33	1.30 (0.92-1.84)	*0.14*	419	39	0.95 (0.66-1.37)	*0.79*
Change from baseline to month-1[b]	372	23	1.92 (1.11-3.30)	*0.019*	366	25	1.20 (0.66-2.18)	*0.55*
CRP								
Baseline	456	37	1.29 (0.94-1.76)	*0.11*	456	40	1.37 (1.07-1.75)	*0.012*
Change from baseline to month-1[b]	403	25	1.19 (0.78-1.81)	*0.41*	396	26	1.17 (0.69-1.98)	*0.55*
Unadjusted change from baseline to month-3[c]	354	14	2.03 (1.14-3.60)	*0.016*	342	16	0.64 (0.32-1.28)	*0.21*

[a] all predictors were log transformed except for the changes from baseline to month-1

[b] adjusted for baseline values

[c] adjusted for baseline values and change from baseline to month-1

[d] Per 1-unit standard deviation increase

Supplemental Table 3. Unadjusted association between biomarkers and VTE in placebo group

Predictor[a]	**N**	**VTE**		
		N of events	**SHR (95% CI)**[d]	***p-value***
GDF-15				
Baseline	256	30	1.29 (0.95-1.76)	*0.10*
Change from baseline to month-1[b]	231	23	1.22 (0.86-1.74)	*0.27*
NT-ProBNP				
Baseline	256	30	1.01 (0.70-1.45)	*0.97*
Change from baseline to month-1[b]	231	23	1.06 (0.72-1.56)	*0.78*
hs-TnT				
Baseline	256	30	1.27 (0.91-1.77)	*0.16*
Change from baseline to month-1[b]	231	23	2.71 (1.27-5.81)	*0.010*
CRP				
Baseline	256	30	1.13 (0.82-1.57)	*0.46*
Change from baseline to month-1[b]	231	23	1.27 (0.77-2.10)	*0.34*
Change from baseline to month-3[c]	190	12	2.02 (1.09-3.76)	*0.026*

[a] all predictors were log transformed except for the changes from baseline to month-1

[b] adjusted for baseline values

[c] adjusted for baseline values and change from baseline to month-1

[d] Per 1-unit standard deviation increase

Supplemental Table 4. Unadjusted association between biomarkers and clinically relevant bleeding in apixaban group

Predictor[a]	**N**	**Clinically Relevant Bleeding**		
		N of events	**SHR (95% CI)**[d]	***p-value***
GDF-15				
Baseline	258	30	1.15 (0.80-1.66)	*0.44*
Change from baseline to month-1[b]	217	17	1.37 (0.69-2.72)	*0.37*
NT-ProBNP				
Baseline	258	30	1.58 (1.15-2.18)	*0.005*
Change from baseline to month-1[b]	217	17	1.17 (0.79-1.75)	*0.42*
hs-TnT				
Baseline	258	30	1.12 (0.81-1.56)	*0.50*
Change from baseline to month-1[b]	217	17	1.26 (0.65-2.45)	*0.42*
CRP				
Baseline	258	30	1.46 (1.13-1.89)	*0.004*
Change from baseline to month-1[b]	217	18	1.03 (0.59-1.80)	*0.92*
Change from baseline to month-3[c]	181	11	0.66 (0.30-1.47)	*0.31*

[a] all predictors were log transformed except for the changes from baseline to month-1

[b] adjusted for baseline values

[c] adjusted for baseline values and change from baseline to month-1

[d] Per 1-unit standard deviation increase

Supplemental Table 5. Association between CRP change subgroups and risk of VTE and clinically relevant bleeding

Predictor[a]	**Model**	**VTE**			**Clinically Relevant Bleeding**		
		N of events	**SHR (95% CI)[d]**	***p-value***	**N of events**	**SHR (95% CI)[d]**	***p-value***
CRP change subgroups*							
CRP rise	Unadjusted	14	1.27 (0.36-4.54)	*0.71*	16	1.02 (0.30-3.55)	*0.97*
	Adjusted	14	1.13 (0.28-4.48)	*0.86*	16	1.17 (0.33-4.14)	*0.81*
CRP decline	Unadjusted	14	0.34 (0.12-0.96)	*0.042*	16	1.43 (0.47-4.41)	*0.53*
	Adjusted	14	0.33 (0.11-1.02)	*0.054*	16	1.30 (0.40-4.25)	*0.66*

***the CRP measurements at month-1 and month-3 were used to classify the subgroups; patients with a doubling or 50% decrease from baseline to month-1 OR month-3 were classified as CRP rise and CRP decline, respectively.**

Chapter 6

Machine learning models for predicting the 7-month risk of venous thromboembolism and clinically relevant bleeding in ambulatory patients with cancer

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Preface to Chapter 6

This Chapter reports machine learning models using data from the AVERT trial for predicting venous thromboembolism (VTE) and clinically relevant bleeding in patients with cancer. While primary thromboprophylaxis can reduce VTE risk, it also increases bleeding risk, highlighting the need for accurate and individualized risk stratification. Given the limitations of existing clinical prediction models, this study explores the potential of machine learning approaches,

incorporating routinely available clinical variables as well as biomarkers and genetic risk factors, to improve personalized thromboprophylaxis strategies.

6.1 Abstract

Background: Patients with cancer are at an elevated risk of venous thromboembolism (VTE). While primary thromboprophylaxis reduces VTE incidence, it also increases bleeding risk, necessitating accurate risk stratification. Existing tools, such as the Khorana score, have modest predictive value, and bleeding risk models have not been validated in ambulatory cancer patients.

Objectives: To train machine learning models for predicting VTE and clinically relevant bleeding in ambulatory cancer patients initiating chemotherapy.

Methods: We used data from 514 participants in the Apixaban for the Prevention of Venous Thromboembolism in High-risk Ambulatory Cancer Patients (AVERT) randomized controlled trial. This trial included cancer patients at intermediate to high risk for VTE (defined as a Khorana score ≥2). Outcomes included objectively confirmed VTE and clinically relevant bleeding over 7 months. For each outcome, we trained three models: logistic regression with L1 regularization and two XGBoost models (one using all available variables, including biomarkers and genetic data; one using only routinely collected variables). Performance was evaluated using optimism-adjusted area under the operating curve (AUC), precision-recall AUC, calibration, and diagnostic statistics.

Results: VTE and clinically relevant bleeding occurred in 8.4% and 9.0% of patients, respectively. The full-variable XGBoost model performed best (VTE AUC: 0.92, bleeding AUC: 0.90). Key VTE predictors included Factor V Leiden, topoisomerase inhibitor use, apixaban, stomach or pancreatic cancer, hemoglobin and high-sensitivity troponin T whereas top bleeding predictors included extracellular vesicles-procoagulant activity, N-terminal pro-B-type natriuretic peptide, C-reactive protein, age, body mass index and blood counts.

Conclusions: Machine learning models incorporating biomarker and genetic variables accurately predicted VTE and clinically relevant bleeding in cancer patients with a Khorana score ≥2, supporting personalized thromboprophylaxis in cancer care.

6.2 Introduction

Patients with cancer have an increased risk of venous thromboembolism (VTE) compared to the general population,[1] particularly during the first six months after initiating chemotherapy.[2,3] The occurrence of VTE in patients with cancer can adversely affect their quality of life,[4] increase their risk of death[5] and lead to higher healthcare costs.[3] Effective primary prevention strategies such as pharmacological thromboprophylaxis are thus desired, however, given the risk of bleeding complications associated with anticoagulation therapy, they are ideally only given to the highest risk patients (i.e., those most likely to benefit). This is supported by current guidelines which suggest the use of primary thromboprophylaxis with apixaban or rivaroxaban in ambulatory cancer patients with intermediate to high-risk of VTE.[6–8]

To identify ambulatory patients with cancer at higher risk of VTE who would benefit from primary thromboprophylaxis, various risk assessment tools have been developed, with the Khorana score being the most widely used and recommended by clinical guidelines.[9] The Khorana score stratifies patients with cancer into low risk (0 points), intermediate risk (1-2 points) and high risk (3 or more points) based on clinical factors.[9] Guidelines generally recommend thromboprophylaxis in patients with a Khorana score of ≥2 since primary thromboprophylaxis has been shown to reduce VTE incidence in these patients without significantly increasing the risk of bleeding, as shown in the AVERT and CASSINI trials.[10,11] However, a Khorana score threshold of ≥2 alone may not be optimal in identifying patients with cancer who would benefit most from thromboprophylaxis, as the incidence of VTE in this category is approximately 9-10%,[10–12] and primary thromboprophylaxis might expose many to unnecessary bleeding risks. The suboptimal predictive capacity (i.e., low positive predictive value) of the Khorana score has likely led to an under-utilization of both the Khorana score and primary thromboprophylaxis by clinicians as reported by Martin et al[13] and Mongelli et al[14], despite the recommendations in current guidelines. Therefore, enhancing VTE and bleeding risk prediction is warranted to better identify high-risk patients and optimize thromboprophylaxis strategies.

Other risk assessment scores have been proposed to improve the prediction of cancer-associated VTE, including, the Vienna CATS[15], Protecht[16], Conko[17], COMPASS-CAT[18], CATS/MICA[19], TiC-Onco[20] and ONCOTHROMB[21] scores. However, external validation studies have shown that the majority of these scores have suboptimal discriminatory performance, with

c-statistics between 0.50 to 0.70.[22–28] More recently, a novel electronic health record (EHR)-based VTE risk score has shown improved performance compared to the original Khorana score, though its c-statistic remained modest, between 0.68-0.71, in external validation.[29,30] Researchers have also begun exploring machine learning models to optimize VTE prediction in patients with cancer, although most were specific to a particular patient population, such as those with a specific cancer type or undergoing a procedure, or simply remained suboptimal with poor model performance.[31]

As an alternative to VTE prediction, bleeding risk prediction has also emerged as an active area of research to assist clinicians in the evaluation of the benefits and risks of anticoagulation in ambulatory patients with cancer. An external validation study has evaluated the performance of five commonly used bleeding risk models (i.e., VTE-bleed, AF-bleed, HAS-BLED, ATRIA and ORBIT) in patients with cancer on anticoagulation in the primary care setting.[32] The results showed that these available models could not accurately predict bleeding in these patients,[32] which could be related to the fact that these models were mainly derived for other patient populations such as non-cancer patients with atrial fibrillation or VTE.[33–37] Two other bleeding risk assessment models specific for patients with cancer-associated thrombosis have also been developed (i.e., CAT-BLEED and B-CAT),[38,39] but they have yet to be externally validated. Given that these models were developed in patients receiving therapeutic doses of anticoagulation (and not prophylactic) and the previous models developed for VTE patient populations did not fully translate to cancer patients, it is possible that these newer models may also not be suitable. Due to the lack of a validated and reliable bleeding risk model, current guidelines do not recommend a specific bleeding risk assessment tool, underscoring an important evidence gap.

In hopes of improving VTE and bleeding prediction in ambulatory patients with cancer and thromboprophylaxis decision-making, in this study, we trained machine learning models in ambulatory patients with cancer starting chemotherapy. In the machine learning models, we incorporated biomarkers and genetic variables, given previous evidence supporting their use in prediction of VTE and bleeding outcomes in patients with cancer.[15,20,21,40–42] Biomarkers may serve as indicators of the preclinical phase of VTE or bleeding events in patients at risk, potentially allowing to determine high-risk patients before the onset of outcomes. Similarly, genes involved in inherited thrombophilia, which affect coagulation, may be valuable predictors

given their strong association with coagulability outcomes and time-invariant influence on the development of VTE or bleeding.

6.3 Methods

The Ottawa Health Science Network Research Ethics Board has reviewed and approved this study (20240294-01H). This article was developed following the guidelines outlined by the EQUATOR Network for reporting machine learning predictive models in biomedical research and the TRIPOD+AI guidelines.[43,44]

Study design and setting

We developed machine learning models using data from the Apixaban to Prevent Venous Thromboembolism in Cancer (AVERT) trial.[11] The AVERT trial was a multicenter, randomized, double-blinded, placebo-controlled trial comparing the efficacy of apixaban vs placebo for preventing VTE in ambulatory patients with cancer starting chemotherapy. A total of 574 patients were enrolled in the AVERT trial between February 2014 to April 2018 from 13 Canadian hospitals. The AVERT trial enrolled adult patients (≥18 years old) with newly diagnosed or progressive cancer with a Khorana score of 2 or more who were starting chemotherapy. The exclusion criteria for the AVERT trial included: patients with a diagnosis of acute leukemia, myeloproliferative neoplasms, basal-cell or squamous-cell skin carcinoma (as the only cancer diagnosis), hepatic disease associated with coagulopathy or conditions that increase the patient's risk for clinically significant bleeding; patients with a planned stem-cell transplantation, life expectancy less han 6 months, renal insufficiency (glomerular filtration rate of less than 30ml per minute per 1.73m^2 of body surface area), a weight less than 40kg or platelet count less than 50,000 per cubic millimeter, patients who were already on anticoagulation, pregnant and breast feeding.

Outcome and predictor variables

The outcomes we used in this analysis were first VTE and bleeding events occurring within 7-months after enrollment. VTE was defined as objectively confirmed symptomatic or incidentally detected thromboembolic events, including proximal or distal lower or upper limb deep vein thrombosis (DVT), pulmonary embolism (PE), splanchnic or cerebral vein thrombosis occurring

within 7 months following enrollment. Routine ultrasounds were not performed; only patients who presented with symptoms of VTE underwent imaging for outcome assessment. Clinically relevant bleeding was defined as the composite of major bleeding and clinically relevant nonmajor bleeding (CRNMB) (both defined using the International Society on Thrombosis and Haemostasis definitions) events[45,46]. During the AVERT trial, all outcomes were adjudicated by a outcome adjudication committee blinded to treatment assignment.

As predictor variables, we included any available baseline variables commonly known as potential risk factors for VTE or clinically relevant bleeding events. The predictor variables included a combination of demographic, clinical and laboratory variables. The full list of variables is reported in Supplementary Table 1 and defined in Supplementary Table 2. We combined cancer type and cancer stage into advanced solid (i.e., stage 3 or 4), non-advanced solid (i.e., stage 1 or 2) and hematological cancer due to sparsity of certain cancer types and to avoid potential collinearity between cancer types and stages. Additionally, high-risk antimetabolites use was considered present if a patient received capecitabine, fluorouracil or gemcitabine as part of their chemotherapy regimen - agents thought to be associated with increased VTE risk - and absent if none of these were used. All demographic and clinical data, as well as routine laboratory data were collected during the AVERT trial. Additional biomarkers not currently available in routine clinical practice were measured using the AVERT baseline samples stored for secondary use research. The laboratory methods/assays for these variables are described in their respective article and summarized in Supplementary Table 2.

Statistical Analysis

We assessed patient characteristics and laboratory biomarker levels using descriptive statistics and histograms. Biomarkers which were right skewed were log-transformed, and thereafter, all continuous variables were standardized by subtracting the mean and dividing by the standard deviation (SD). Missing data was imputed using single imputation predictive mean matching. To assess the robustness of the results, we performed a sensitivity analysis using a second imputation dataset. No formal sample size calculation was performed for this study since the current study relied on data that had already been collected.

We compared two modeling strategies: logistic regression with L1/LASSO regularization and extreme gradient boosting (XGBoost). Logistic regression with L1 regularization is a

method that penalizes coefficient estimates and effectively shrinks coefficients estimates of less important variables toward zero, thereby performing variable selection. On the other hand, XGBoost is an ensemble learning method that sequentially constructs a series of decision trees (for regression or classification) using gradient boosting, where each tree is built iteratively to correct the errors made by the previous ones. XGBoost is known as a dominant machine learning algorithm given its ability to incorporate regularization and capture important interactions, all while being highly efficient and flexible. A logistic regression with L1 regularization model was developed for each outcome (i.e., VTE and clinically relevant bleeding), while two XGBoost models were constructed for each outcome: one using all available biomarker/genetic predictors and another incorporating only predictors routinely measured as part of standard practice.

We performed stratified 5-fold cross validation to determine the optimal penalty term for logistic regression with L1 regularization and hyperparameters (i.e., boosting iterations, learning rate, gamma, lambda, alpha, tree depth, instance weight sum and percentage of rows and columns used for tree construction) for XGBoos. Stratification ensured that the proportion of events was similar across folds. The models with the best performance were selected as the final models. The final models were compared and internally validated using standard bootstrap validation and optimism-adjusted performance measures, including area under the ROC curve (AUC), Precision-Recall AUC (PRAUC), Log loss and Brier scores. We also reported optimism-adjusted sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) using a predicted risk threshold of 10%, chosen based on the ESMO guidelines, which suggests 8-10% as a threshold for discussing thromboprophylaxis.[47] Consecutively, optimism-adjusted confusion matrix measures were calculated for increasing predicted risk thresholds (i.e., 15% and 20%) and we estimated the predicted risk threshold, specificity, NPV and PPV when the model sensitivity was set at 80% to facilitate comparability. Moreover, we assessed model calibration using a calibration slope, which was determined using a regression slope of the smoothed observed vs predicted probabilities. Lastly, to improve model explainability, we determined the Odds Ratio (OR) for the most important features in the logistic regression models and generated Shapley Additive exPlanations (SHAP) value plots for the XGBoost models. All analyses were conducted using R Studio (R Foundation for Statistical Computing, R Core Team (2024) Vienna, Austria) and the *glmnet,*[48,49] *xgboost*[50] and *boot*[51,52] R packages.

6.4 Results

514 of 574 AVERT trial patients consented to providing blood samples for secondary use research. Patients who did not consent to secondary use research were excluded (n=60). The mean age was 61.2 (± 12.0) and 58% were female (Table 1). A total of 258 (50%) were patients randomized to apixaban. The most common primary cancer sites were gynecologic (27%), lymphoma (25%), pancreatic (13%) and gastrointestinal (11%) (Table 1). Most patients had advanced cancer (81%) (Table 1). During the 7-month follow-up, 27.0%, 23.4%, 6.4% and 2.3% patients underwent targeted therapy, radiotherapy, hormonal therapy and surgery, respectively. During the median follow-up of 196 days, the VTE and clinically relevant bleeding incidence rates were 8.4% (n=43) and 9.0% (n=46), respectively. The majority of VTE events were lower extremity DVT (n=15), upper extremity DVT (n=9) and/or PE (n=15), with two patients experiencing combined DVT and PE, and two splanchnic vein thrombosis. Out of the 46 clinically relevant bleeding events, 11 were major bleeding and 35 were CRNMB. The proportion of missing data ranged from 1.6% to 16.1% (Table 1).

Three models were developed for both VTE and clinically relevant bleeding events: logistic regression with L1 regularization, XGBoost using all available variables (Model A) and XGBoost using only variables measured as part of standard practice (Model B). Table 2 and 3 presents the optimism-adjusted performance and accuracy measures for the different VTE and bleeding models. For the VTE outcome, the XGBoost Model A achieved the highest discrimination (optimism-adjusted AUC: 0.91 [95% CI: 0.86-0.95] and PRAUC: 0.70 [95% CI: 0.55-0.78]) and had the lowest Log loss and Brier score (optimism-adjusted Log loss: 0.23 [95% CI: 0.20-0.27] and Brier score: 0.06 [95% CI: 0.05-0.08]), indicating better calibration (Table 2). Using a predicted threshold of 10%, the optimism-adjusted sensitivity, specificity, NPV and PPV of the XGBoost Model A were 91%, 67%, 99% and 14%, respectively (Table 3). As expected, with increasing values of predicted risk thresholds, the sensitivity decreased and specificity increased (Table 2). At a sensitivity of 80%, this model had a specificity of 93%, an NPV of 98% and a PPV of 51%, at a predicted risk threshold of 16% (Supplemental Table 3).

For the clinically relevant bleeding outcome, the XGBoost Model A also had the best performance with the highest discrimination (optimism-adjusted AUC: 0.90 [95% CI: 0.86-0.93] and PRAUC: 0.70 [95% CI: 0.56-0.78]) and lowest Log loss and Brier score (optimism-adjusted Log loss: 0.27 [95% CI: 0.23-0.30] and Brier score: 0.08 [95% CI: 0.06-0.09]) (Table 2).

However, notably, the performance measures of the XGBoost Model B were close to that of XGBoost Model A. The optimism-adjusted AUC, PRAUC, Log loss and Brier score for the XGBoost Model B were 0.88 (95% CI: 0.84-0.91), 0.54 (95% CI: 0.38-0.64), 0.26 (95% CI: 0.22-0.30) and 0.08 (95% CI: 0.06-0.09), respectively (Table 2). At a sensitivity of 80%, the XGBoost Model A had a specificity of 90%, an NPV of 98% and a PPV of 45% whereas the XGBoost Model B had a specificity of 84%, NPV of 98% and PPV of 32% (Supplemental Table 3). Our sensitivity analyses using a second imputed dataset revealed similar performance measures for all six models (Supplementary Table 4).

A calibration plot was generated for both XGBoost models (Model A and Model B) to assess calibration for both outcomes (Figure 1). All four models had good calibration at lower levels of observed vs predicted probabilities (approximately 0 to 30%), but had lower agreement for higher predicted probabilities, likely due to limited patients with high predicted probabilities.

The most important variables with non-zero coefficients in the logistic regression model for VTE included factor V Leiden (FVL) mutation (OR: 3.40), gastric or pancreatic cancer (1.96), use of topoisomerase inhibitors (OR: 1.56), apixaban use (OR: 0.70), extracellular vesicles (EV) procoagulant activity (OR: 1.09) and d-dimer (1.06). For clinically relevant bleeding, the important variables were C-reactive protein (CRP) (OR: 1.20), apixaban use (OR: 1.18), C-X-C motif chemokine ligand 12 (also known as a chemokine that regulates tissue hemostasis and inflammatory responses) (OR: 1.07), F11 gene mutation (OR: 1.06) and hemoglobin (OR: 0.95). For the XGBoost models, the most important variables are summarized using SHAP value plots in decreasing order of importance (Supplementary Figures 1-4). The features with the highest average SHAP impact included FVL, use of topoisomerase inhibitors, apixaban use, gastric or pancreatic cancer, hemoglobin and high-sensitivity troponin T (hs-TnT) for VTE and, extracellular vesicles (EV)-procoagulant activity, N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), age, body mass index (BMI) and platelet and white blood counts for clinically relevant bleeding.

6.5 Discussion

In ambulatory patients with cancer, the decision to initiate primary thromboprophylaxis is complex and further complicated by the risk of anticoagulant-related clinically relevant bleeding. To aid in this decision-making, we trained and internally validated machine learning models to

predict the risks of both VTE and clinically relevant bleeding events in ambulatory patients with cancer and a Khorana score of 2 or more using the AVERT patient cohort. For both outcomes, the XGBoost model incorporating all variables including biomarkers not currently measured in routine clinical practice and genetic variables (model A) had the highest discriminatory performance. However, the XGBoost model based solely on variables available in routine practice (model B) showed similar performance for the prediction of clinically relevant bleeding. Key VTE predictors that appeared as important variables included FVL, use of topoisomerase inhibitors, apixaban use, gastric or pancreatic cancer, hemoglobin and hs-TnT, whereas top predictors for bleeding events included EV-procoagulant activity, NT-proBNP, CRP, platelet and white blood counts.

These results highlight the potential of machine learning models to refine risk prediction of VTE and clinically relevant bleeding in patients with cancer. Our models, particularly Model A, achieved impressive optimism-adjusted performance measures, surpassing the performance measures of existing risk models in ambulatory cancer patients. In particular, previous studies using machine learning algorithms to predict VTE in ambulatory patients with cancer had AUCs ranging from 0.68 to 0.84[31] and existing risk scores (i.e., Khorana score, VIENNA CATS, Protecht, Conko, Onkotev, COMPASS-CAT, ONCOTHROMB and a EHR-integrated score) had AUCs predominantly ranging from 0.50 to 0.70.[5,20–26,28,30,53–58] Notably, both of our XGBoost bleeding machine learning models had greater AUCs (i.e., 0.90 and 0.88) than existing bleeding risk models, which were approximately 0.56 when validated in patients with cancer.[32] The low performance of these other bleeding risk models may be explained by the fact that many were derived to predict major bleeding events specifically, and were often derived in other patient populations distinct from those with cancer, including individuals with atrial fibrillation, non-cancer patients with VTE or those receiving different oral anticoagulant dosing regimens. [33–37] Thus, to our knowledge, we are the first to develop and internally validate machine learning bleeding risk models specifically for cancer patients initiating chemotherapy who have not yet had a VTE event, offering a more tailored approach to managing the risk of bleeding in this patient population.

Our results also highlight the value of incorporating genetic and non-standard biomarker data not yet available in routine practice into prediction models to improve accuracy, as evidenced by the higher overall predictive performance of the XGBoost Model A compared to

XGBoost Model B, though this was more prominent for VTE. This is consistent with previous studies which have incorporated genetic and/or biomarker data with clinical data to improve the prediction of VTE in patients with cancer. [15,20,21,40–42] We found that biomarkers such as FVL, hs-TnT, active plasminogen activator inhibitor (PAI-1), EV-procoagulant activity and D-dimer were amongst the top VTE predictors included in the final model. While the mechanisms and predictive ability of FVL, PAI-1, EV-procoagulant activity and D-dimer are well-established,[40,59–62] the association between the risk of VTE and hs-TnT in patients with cancer is more novel and warrants further investigation. Additionally, clinical variables such as gastric and pancreatic cancer, and the use of topoisomerase inhibitors and apixaban commonly appeared as important variables in all three VTE models. In contrast, biomarkers that were amongst the top bleeding predictors in the final XGBoost Model A included EV-procoagulant activity, NT-proBNP, and CRP, D-dimer. However, since biomarkers for predicting bleeding events in patients with cancer have been far less explored, the clinical relevance and mechanisms behind these predictors require additional research. The important clinical predictors for clinically relevant bleeding identified in the models (i.e., BMI, age, platelet and white blood counts) are supported by the literature as predictors of bleeding events in patients with cancer.[32,63–65]

The machine learning models developed in this study may have clinical implications to help determine a patient's risk of VTE and clinically relevant bleeding, but their application in clinical practice would require external validation. Future work should focus on further validation and potential refinement of these models to ensure they are applicable to a broader cancer patient population. Our models also provide a unique approach to estimating the risk of VTE and clinically relevant bleeding since we included a variable for patients randomized to the apixaban group during the AVERT trial. Thus, with our models, one could estimate the risk of VTE and clinically relevant bleeding should they receive apixaban, offering personalized decision support for anticoagulation therapy. Ultimately, these models could help guide clinicians in making more informed decisions about primary thromboprophylaxis, if proven accurate in external validation studies.

A major strength of this study is that we addressed some of the shortcomings identified in other machine learning studies, including clearly defining the follow-up period, the timing of model acquisition, assessing for collinearity and using imputation methods instead of excluding missing data.[31] Nevertheless, the study has some limitations. First, the relatively modest sample

size may limit the robustness of the machine learning models, as larger datasets are often recommended. Additionally, the models were developed using patients with a Khorana score of 2 or more, which may limit the generalizability of our results to all cancer patients. Thirdly, we observed poor calibration at higher predicted risk thresholds (e.g., >35%), reducing the reliability of the models in estimating the true risk for the very high-risk patients. However, since an 8-10% threshold has historically been suggested for consideration of thromboprophylaxis,[47] this may be of less concern. Moreover, external validation will be needed for further validation of the models. Finally, while the XGBoost Model A for both outcomes demonstrated high discriminatory performance, its practicality in clinical practice may be limited by the fact that it incorporated predictors that are not routinely measured in clinical practice. An alternative would be to use the XGBoost Models B, which may be suitable for predicting clinically relevant bleeding as the performance of the model remained high albeit less accurate for predicting VTE.

In conclusion, we developed and internally validated machine learning models to predict the risk of VTE and clinically relevant bleeding events in ambulatory cancer patients with a Khorana score of 2 or higher. Some genetic and biomarkers, which are not yet available in routine clinical practice, did help to improve the prediction of the models. If proven accurate in external validation studies, these models may help clinicians in making informed decisions about primary thromboprophylaxis.

6.6 References

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Table 1. Patient characteristics and laboratory variables overall and by outcome

Variable	Overall (N=514)	VTE		Clinically Relevant Bleeding	
		No (N=471)	Yes (N=43)	No (N=468)	Yes (N=46)
Age, years					
Mean (SD)	61.2 (± 12.0)	61.1 (± 12.1)	62.4 (± 11.1)	61.3 (± 11.8)	60.5 (± 14.7)
Median (min-max)	62.0 (21.0-88.0)	62.0 (21.0-88.0)	64.0 (25.0-80.0)	62.0 (21.0-88.0)	62.5 (26.0-85.0)
Sex					
Female	299 (58 %)	276 (59 %)	23 (53 %)	268 (57 %)	31 (67 %)
Male	215 (42 %)	195 (41 %)	20 (47 %)	200 (43 %)	15 (33 %)
BMI, kg/m^2					
Mean (SD)	29.4 (± 7.5)	29.4 (± 7.5)	29.4 (± 7.4)	29.4 (± 7.3)	29.8 (± 9.1)
Median (min-max)	27.7 (16.4-59.8)	27.7 (16.4-59.8)	27.5 (18.9-55.4)	27.7 (16.8-59.8)	27.7 (16.4-53.5)
Apixaban Use					
Yes	258 (50 %)	245 (52 %)	13 (30 %)	228 (49 %)	30 (65 %)
No	256 (50 %)	226 (48 %)	30 (70 %)	240 (51 %)	16 (35 %)
NSAID Use					
Yes	80 (16 %)	74 (16 %)	6 (14 %)	70 (15 %)	10 (22 %)
No	434 (84 %)	397 (84 %)	37 (86 %)	398 (85 %)	36 (78 %)
Antiplatelet Use					
Yes	107 (21 %)	100 (21 %)	7 (16 %)	97 (21 %)	10 (22 %)
No	407 (79 %)	371 (79 %)	36 (84 %)	371 (79 %)	36 (78 %)
Previous VTE					
Yes	16 (3 %)	13 (3 %)	3 (7 %)	14 (3 %)	2 (4 %)

Variable	Overall (N=514)	VTE		Clinically Relevant Bleeding	
		No (N=471)	Yes (N=43)	No (N=468)	Yes (N=46)
No	498 (97 %)	458 (97 %)	40 (93 %)	454 (97 %)	44 (96 %)
Primary Cancer					
Brain	22 (4 %)	19 (4 %)	3 (7 %)	21 (4 %)	1 (2 %)
Breast	17 (3 %)	17 (4 %)	0 (0 %)	16 (3 %)	1 (2 %)
Gastrointestinal	59 (11 %)	50 (11 %)	9 (21 %)	54 (12 %)	5 (11 %)
Gynecologic	138 (27 %)	130 (28 %)	8 (19 %)	121 (26 %)	17 (37 %)
Hematological	17 (3 %)	17 (4 %)	0 (0 %)	16 (3 %)	1 (2 %)
Lung	51 (10 %)	51 (11 %)	0 (0 %)	49 (10 %)	2 (4 %)
Lymphoma	131 (25 %)	123 (26 %)	8 (19 %)	119 (25 %)	12 (26 %)
Other	12 (2 %)	9 (2 %)	3 (7 %)	11 (2 %)	1 (2 %)
Pancreas	67 (13 %)	55 (12 %)	12 (28 %)	61 (13 %)	6 (13 %)
Advanced cancer					
No	55 (11 %)	50 (11 %)	5 (12 %)	54 (12 %)	1 (2 %)
Yes	416 (81 %)	384 (82 %)	32 (74 %)	375 (80 %)	41 (89 %)
Missing	43 (8.4%)	37 (7.9%)	6 (14.0%)	39 (8.3%)	4 (8.7%)
Khorana Score					
2	338 (66 %)	315 (67 %)	23 (53 %)	308 (66 %)	30 (65 %)
3	135 (26 %)	120 (25 %)	15 (35 %)	124 (26 %)	11 (24 %)
4	41 (8 %)	36 (8 %)	5 (12 %)	36 (8 %)	5 (11 %)
Platinum-based chemotherapy					
No	252 (49 %)	234 (50 %)	18 (42 %)	229 (49 %)	23 (50 %)
Yes	262 (51 %)	237 (50 %)	25 (58 %)	239 (51 %)	23 (50 %)

Variable	Overall (N=514)	VTE		Clinically Relevant Bleeding	
		No (N=471)	Yes (N=43)	No (N=468)	Yes (N=46)
Taxane-based chemotherapy					
No	326 (63 %)	295 (63 %)	31 (72 %)	299 (64 %)	27 (59 %)
Yes	188 (37 %)	176 (37 %)	12 (28 %)	169 (36 %)	19 (41 %)
Anthracycline-based chemotherapy					
No	407 (79 %)	373 (79 %)	34 (79 %)	373 (80 %)	34 (74 %)
Yes	107 (21 %)	98 (21 %)	9 (21 %)	95 (20 %)	12 (26 %)
Topoisomerase-based chemotherapy					
No	458 (89 %)	426 (90 %)	32 (74 %)	414 (88 %)	44 (96 %)
Yes	56 (11 %)	45 (10 %)	11 (26 %)	54 (12 %)	2 (4 %)
High-risk antimetabolites					
No	372 (72 %)	351 (75 %)	21 (49 %)	340 (73 %)	32 (70 %)
Yes	142 (28 %)	120 (25 %)	22 (51 %)	128 (27 %)	14 (30 %)
ABO gene					
Non-O blood type	270 (53 %)	240 (51 %)	30 (70 %)	249 (53 %)	21 (46 %)
O blood type	175 (34 %)	166 (35 %)	9 (21 %)	160 (34 %)	15 (33 %)
Missing	69 (13.4%)	65 (13.8%)	4 (9.3%)	59 (12.6%)	10 (21.7%)
F5 gene, FVL					
Mutated	20 (4 %)	13 (3 %)	7 (16 %)	20 (4 %)	0 (0 %)
Normal	426 (83 %)	394 (84 %)	32 (74 %)	390 (83 %)	36 (78 %)

Variable	Overall (N=514)	VTE		Clinically Relevant Bleeding	
		No (N=471)	Yes (N=43)	No (N=468)	Yes (N=46)
Missing	68 (13.2%)	64 (13.6%)	4 (9.3%)	58 (12.4%)	10 (21.7%)
F13 gene					
Mutated	194 (38 %)	178 (38 %)	16 (37 %)	177 (38 %)	17 (37 %)
Normal	251 (49 %)	229 (49 %)	22 (51 %)	232 (50 %)	19 (41 %)
Missing	69 (13.4%)	64 (13.6%)	5 (11.6%)	59 (12.6%)	10 (21.7%)
F5 gene, K858R					
Mutated	199 (39 %)	183 (39 %)	16 (37 %)	184 (39 %)	15 (33 %)
Normal	248 (48 %)	225 (48 %)	23 (53 %)	227 (49 %)	21 (46 %)
Missing	67 (13.0%)	63 (13.4%)	4 (9.3%)	57 (12.2%)	10 (21.7%)
SERPINA10 gene					
Mutated	3 (1 %)	3 (1 %)	0 (0 %)	3 (1 %)	0 (0 %)
Normal	443 (86 %)	404 (86 %)	39 (91 %)	407 (87 %)	36 (78 %)
Missing	68 (13.2%)	64 (13.6%)	4 (9.3%)	58 (12.4%)	10 (21.7%)
FGG gene					
Mutated	183 (36 %)	169 (36 %)	14 (33 %)	165 (35 %)	18 (39 %)
Normal	259 (50 %)	235 (50 %)	24 (56 %)	241 (51 %)	18 (39 %)
Missing	72 (14.0%)	67 (14.2%)	5 (11.6%)	62 (13.2%)	10 (21.7%)
F11 gene					
Mutated	339 (66 %)	307 (65 %)	32 (74 %)	309 (66 %)	30 (65 %)
Normal	108 (21 %)	101 (21 %)	7 (16 %)	102 (22 %)	6 (13 %)
Missing	67 (13.0%)	63 (13.4%)	4 (9.3%)	57 (12.2%)	10 (21.7%)
F2 gene, Prothrombin G20210A					

Variable	Overall (N=514)	VTE		Clinically Relevant Bleeding	
		No (N=471)	Yes (N=43)	No (N=468)	Yes (N=46)
Mutated	9 (2 %)	8 (2 %)	1 (2 %)	9 (2 %)	0 (0 %)
Normal	438 (85 %)	400 (85 %)	38 (88 %)	402 (86 %)	36 (78 %)
Missing	67 (13.0%)	63 (13.4%)	4 (9.3%)	57 (12.2%)	10 (21.7%)
Platelet Count, x 10^9/L					
Mean (SD)	320 (± 134)	320 (± 134)	320 (± 137)	317 (± 129)	354 (± 175)
Median (min-max)	313 (70.0-1020)	315 (70.0-1020)	292 (99.0-716)	309 (70.0-809)	354 (130-1020)
Hemoglobin, g/L					
Mean (SD)	119 (± 20)	119 (± 19.3)	120 (± 26.8)	120 (± 20.1)	112 (± 17.6)
Median (min-max)	119 (13.0-182)	119 (75.0-182)	124 (13.0-161)	120 (13.0-182)	113 (81.0-156)
Missing	1 (0.2%)	1 (0.2%)	0 (0%)	1 (0.2%)	0 (0%)
White Blood Count, x 10^9/L					
Mean (SD)	13.2 (± 23.2)	13.6 (± 24.2)	9.5 (± 3.5)	13.0 (± 22.8)	15.2 (± 27.7)
Median (min-max)	9.0 (1.0-243)	9.0 (2.0-243)	9.0 (1.0-18.0)	9.0 (1.0-243)	8.8 (4.0-186)
CrCl, mL/min					
Mean (SD)	107 (± 43.0)	107 (± 42.9)	107 (± 45.3)	107 (± 42.8)	108 (± 46.0)
Median (min-max)	99.0 (36.0-281)	99.0 (36.0-266)	97.0 (50.0-281)	99.0 (36.0-281)	105 (39.0-215)
FXIa-C1, nM					
Mean (SD)	1.0 (± 1.3)	1.0 (± 1.3)	1.0 (± 1.2)	1.0 (± 1.3)	0.9 (± 0.8)

Variable	Overall (N=514)	VTE		Clinically Relevant Bleeding	
		No (N=471)	Yes (N=43)	No (N=468)	Yes (N=46)
Median (min-max)	0.7 (0.01-14.4)	0.7 (0.01-14.4)	0.7 (0.01, 6.9)	0.7 (0.01, 14.4)	0.7 (0.03-3.0)
Missing	32 (6.2%)	29 (6.2%)	3 (7.0%)	27 (5.8%)	5 (10.9%)
aPAI-1, U/mL					
Mean (SD)	10.7 (± 15.6)	11.0 (± 16.0)	7.6 (± 9.5)	10.9 (± 16.0)	8.7 (± 10.0)
Median (min-max)	5.4 (0.4-100)	5.4 (0.4- 100)	4.2 (0.7-55.4)	5.2 (0.5-100)	6.5 (0.4-47.3)
Missing	40 (7.8%)	37 (7.9%)	3 (7.0%)	35 (7.5%)	5 (10.9%)
sP-selectin, ng/mL					
Mean (SD)	39.7 (± 18.0)	39.7 (± 17.7)	40.1 (± 20.7)	39.8 (± 18.3)	39.4 (± 14.9)
Median (min-max)	37.4 (2.3-312)	37.4 (2.3-312)	36.8 (3.7-141)	37.4 (2.3-312)	38.2 (3.0-93.0)
Missing	34 (6.6%)	31 (6.6%)	3 (7.0%)	28 (6.0%)	6 (13.0%)
D-dimer, ug/mL					
Mean (SD)	2.3 (± 3.8)	2.2 (± 3.6)	3.6 (± 5.3)	2.2 (± 3.6)	3.2 (± 5.0)
Median (min-max)	1.0 (0.2-20.1)	1.0 (0.2-20.1)	1.6 (0.2-20.1)	1.0 (0.2-20.1)	1.4 (0.3-20.1)
Missing	8 (1.6%)	7 (1.5%)	1 (2.3%)	7 (1.5%)	1 (2.2%)
CRP, mg/dL					
Mean (SD)	2.6 (± 4.3)	2.5 (± 4.2)	3.1 (± 5.1)	2.5 (± 4.4)	3.5 (± 3.6)
Median (min-max)	0.7 (0.3-32.7)	0.7 (0.3-32.7)	0.7 (0.3-27.0)	0.6 (0.3-32.7)	2.2 (0.3-14.7)
Missing	17 (3.3%)	17 (3.6%)	0 (0%)	15 (3.2%)	2 (4.3%)
HGH, ng/mL					

Variable	Overall (N=514)	VTE		Clinically Relevant Bleeding	
		No (N=471)	Yes (N=43)	No (N=468)	Yes (N=46)
Mean (SD)	1150 (± 1780)	1110 (± 1760)	1610 (± 1940)	1120 (± 1750)	1460 (± 2030)
Median (min-max)	508 (29.9-12400)	493 (29.9-12400)	891 (29.9-7470)	502 (29.9-12400)	611 (29.9-10600)
Missing	32 (6.2%)	28 (5.9%)	4 (9.3%)	29 (6.2%)	3 (6.5%)
NT-proBNP, pg/mL					
Mean (SD)	237 (± 459)	240 (± 474)	206 (± 238)	225 (± 454)	363 (± 492)
Median (min-max)	118 (35.9-6310)	117 (35.9-6310)	124 (35.9-1210)	116 (35.9-6310)	157 (35.9-2060)
Missing	31 (6.0%)	27 (5.7%)	4 (9.3%)	28 (6.0%)	3 (6.5%)
hs-TnT, pg/mL					
Mean (SD)	10.2 (± 8.8)	9.8 (± 7.6)	13.8 (± 16.7)	10.2 (± 9.0)	9.9 (± 6.9)
Median (min-max)	7.0 (5.9-92.3)	7.0 (5.9-92.3)	7.5 (5.9-85.6)	7.1 (5.9-92.3)	6.9 (5.9-38.2)
Missing	56 (10.9%)	52 (11.0%)	4 (9.3%)	53 (11.3%)	3 (6.5%)
TSH, uIU/mL					
Mean (SD)	1.4 (± 2.0)	1.5 (± 2.1)	1.3 (± 0.7)	1.4 (± 1.6)	2.1 (± 4.4)
Median (min-max)	1.0 (0.1-28.8)	1.0 (0.1-28.8)	1.2 (0.1- 3.0)	1.0 (0.1-18.8)	1.1 (0.2-28.8)
Missing	31 (6.0%)	27 (5.7%)	4 (9.3%)	28 (6.0%)	3 (6.5%)
GDF-15, pg/mL					
Mean (SD)	1510 (± 1140)	1490 (± 1120)	1760 (± 1290)	1490 (± 1110)	1700 (± 1390)

Variable	Overall (N=514)	VTE		Clinically Relevant Bleeding	
		No (N=471)	Yes (N=43)	No (N=468)	Yes (N=46)
Median (min-max)	1130 (283-6000)	1110 (283-6000)	1360 (407-6000)	1120 (283-6000)	1200 (407-6000)
Missing	28 (5.4%)	26 (5.5%)	2 (4.7%)	25 (5.3%)	3 (6.5%)
CXCL-12, pg/mL					
Mean (SD)	1590 (± 457)	1590 (± 462)	1600 (± 414)	1580 (± 453)	1730 (± 480)
Median (min-max)	1580 (408-3290)	1580 (408-3290)	1600 (776-2460)	1570 (408-3290)	1670 (979-2860)
Missing	83 (16.1%)	78 (16.6%)	5 (11.6%)	77 (16.5%)	6 (13.0%)
Microparticles, nM					
Mean (SD)	13.5 (± 13.7)	13.3 (± 13.9)	15.5 (± 12.0)	13.2 (± 13.0)	16.5 (± 20.4)
Median (min-max)	9.4 (0.01-105)	9.3 (0.01-105)	12.7 (2.77-56.5)	9.5 (0.01-95.9)	9.2 (0.01-105)
Missing	61 (11.9%)	59 (12.5%)	2 (4.7%)	52 (11.1%)	9 (19.6%)

Abbreviations: aPAI-1: active plasminogen activator inhibitor-1;BMI: body mass index; CrCl: creatinine clearance; CRP: C-reactive protein; CXCL-12: C-X-C motif chemokine ligand 12; F2: prothrombin gene; F5: coagulation factor V gene; F13: coagulation factor XIII gene; F11: coagulation factor XI gene; FGG: fibrinogen gamma chain gene; FXIa-C1: activated factor XI-antithrombin complex; GDF-15: growth differentiation factor 15; HGH: human growth hormone; hs-TnT: high-sensitivity troponin T; NSAID: nonsteroidal anti-inflammatory drug; NT-proBNP: N-terminal pro–B-type natriuretic peptide; SD: standard deviation; SERPINA10: serpin family A member 10 gene; sP-selectin: soluble P-selectin; TSH: thyroid-stimulating hormone; VTE: venous thromboembolism.

Table 2. Optimism-adjusted performance measures of the LASSO logistic regression and XGBoost models

Model	Logistic regression	XGBoost (Model A)	XGBoost (Model B)
VTE			
AUROC	0.75 (0.67-0.82)	0.91 (0.86-0.95)	0.85 (0.81-0.88)
PRAUC	0.20 (0.10-0.33)	0.70 (0.55-0.78)	0.32 (0.14-0.45)
Log loss	0.26 (0.21-0.32)	0.23 (0.20-0.27)	0.27 (0.23-0.31)
Brier score	0.07 (0.05-0.09)	0.06 (0.05-0.08)	0.08 (0.06-0.10)
Clinically Relevant Bleeding			
AUROC	0.64 (0.56-0.72)	0.90 (0.86-0.93)	0.88 (0.84-0.91)
PRAUC	0.06 (0.00-0.15)	0.70 (0.56-0.78)	0.54 (0.38-0.64)
Log loss	0.31 (0.25-0.37)	0.27 (0.23-0.30)	0.26 (0.22-0.30)
Brier score	0.08 (0.07-0.11)	0.08 (0.06-0.09)	0.08 (0.06-0.09)

Abbreviations: AUROC= Area under the receiver operating characteristic (ROC) curve; PRAUC= Precision-recall ROC curve; VTE= Venous Thromboembolism

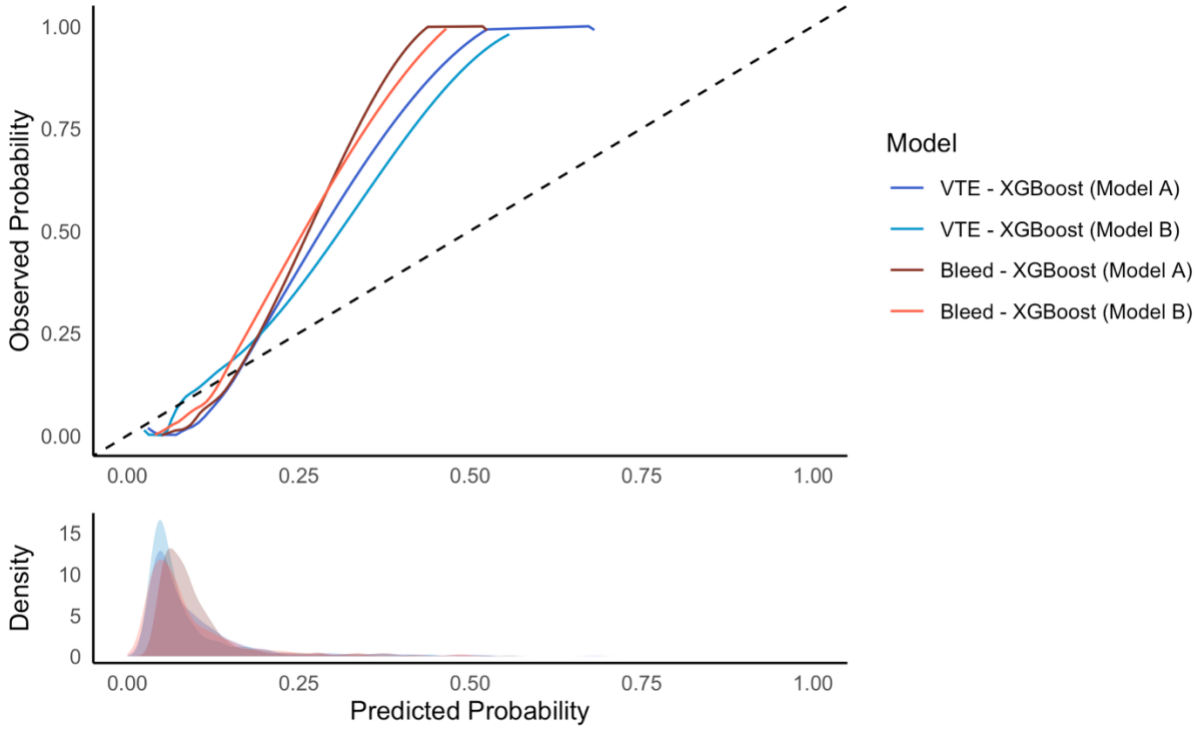
Model - A = all baseline variables; Model – B = only variables measured during standard clinical practice

Table 3. Optimism-adjusted accuracy measures of the XGBoost models

Model	Predicted % Threshold	Sensitivity	Specificity	NPV	PPV
VTE - XGBoost (Model A)	0.10	0.91 (0.79-0.96)	0.67 (0.63-0.71)	0.99 (0.97-1.00)	0.14 (0.08-0.22)
	0.15	0.73 (0.58-0.83)	0.89 (0.87-0.92)	0.97 (0.96-0.98)	0.34 (0.22-0.47)
	0.20	0.56 (0.40-0.69)	0.97 (0.95-0.98)	0.96 (0.94-0.97)	0.61 (0.45-0.74)
VTE - XGBoost (Model B)	0.10	0.63 (0.48-0.75)	0.80 (0.76-0.73)	0.96 (0.94-0.97)	0.19 (0.10-0.28)
	0.15	0.34 (0.18-0.49)	0.90 (0.88-0.93)	0.94 (0.92-0.95)	0.22 (0.09-0.36)
	0.20	0.19 (0.04-0.35)	0.97 (0.95-0.98)	0.93 (0.90-0.95)	0.46 (0.28-0.63)
Clinically Relevant Bleeding - XGBoost (Model A)	0.10	0.92 (0.80-0.97)	0.66 (0.62-0.70)	0.99 (0.97-1.00)	0.16 (0.09-0.24)
	0.15	0.64 (0.49-0.75)	0.94 (0.92-0.96)	0.96 (0.94-0.98)	0.50 (0.36-0.62)
	0.20	0.49 (0.34-0.63)	0.98 (0.97-0.99)	0.95 (0.93-0.97)	0.77 (0.61-0.87)
Clinically Relevant Bleeding - XGBoost (Model B)	0.10	0.81 (0.68-0.89)	0.71 (0.67-0.75)	0.98 (0.96-0.99)	0.18 (0.10-0.26)
	0.15	0.67 (0.52-0.79)	0.91 (0.88-0.93)	0.97 (0.95-0.98)	0.40 (0.28-0.52)
	0.20	0.28 (0.12-0.42)	0.96 (0.94-0.97)	0.93 (0.91-0.95)	0.46 (0.29-0.61)

Model - A = all baseline variables; Model – B = only variables measured during standard clinical practice

Figure 1. Smoothed calibration slope for the XGBoost models



6.7 Appendix

Supplemental Table 1. Summary of patient characteristics and laboratory variables (imputed and standardized data)

Variable	Overall (N=514)	VTE		Clinically Relevant Bleeding	
		No (N=471)	Yes (N=43)	No (N=468)	Yes (N=46)
Age[a], mean (SD)	-0.02 (± 1.00)	-0.03 (± 1.00)	0.08 (± 0.94)	-0.01 (± 0.99)	-0.08 (± 1.20)
Sex					
Female	299 (58 %)	276 (59 %)	23 (53 %)	268 (57 %)	31 (67 %)
Male	215 (42 %)	195 (41 %)	20 (47 %)	200 (43 %)	15 (33 %)
BMI[b], mean (SD)	0.02 (± 1.00)	0.01 (± 1.00)	0.03 (± 0.95)	0.01 (± 0.99)	0.03(± 1.2)
Apixaban Use					
Yes	258 (50 %)	245 (52 %)	13 (30 %)	228 (49 %)	30 (65 %)
No	256 (50 %)	226 (48 %)	30 (70 %)	240 (51 %)	16 (35 %)
NSAID Use					
Yes	80 (16 %)	74 (16 %)	6 (14 %)	70 (15 %)	10 (22 %)
No	434 (84 %)	397 (84 %)	37 (86 %)	398 (85 %)	36 (78 %)
Antiplatelet Use					
Yes	107 (21 %)	100 (21 %)	7 (16 %)	97 (21 %)	10 (22 %)
No	407 (79 %)	371 (79 %)	36 (84 %)	371 (79 %)	36 (78 %)
Previous VTE					
Yes	16 (3 %)	13 (3 %)	3 (7 %)	14 (3 %)	2 (4 %)
No	498 (97 %)	458 (97 %)	40 (93 %)	454 (97 %)	44 (96 %)
Primary Cancer Type Group					
Non-advanced solid	63 (12 %)	56 (12 %)	7 (16 %)	62 (13 %)	1 (2 %)

Variable	Overall (N=514)	VTE		Clinically Relevant Bleeding	
		No (N=471)	Yes (N=43)	No (N=468)	Yes (N=46)
Advanced solid	296 (58 %)	269 (57 %)	27 (63 %)	265 (57 %)	31 (67 %)
Hematological	155 (30 %)	146 (31 %)	9 (21 %)	141 (30 %)	14 (30 %)
Platinum-based chemotherapy					
No	252 (49 %)	234 (50 %)	18 (42 %)	229 (49 %)	23 (50 %)
Yes	262 (51 %)	237 (50 %)	25 (58 %)	239 (51 %)	23 (50 %)
Taxane-based chemotherapy					
No	326 (63 %)	295 (63 %)	31 (72 %)	299 (64 %)	27 (59 %)
Yes	188 (37 %)	176 (37 %)	12 (28 %)	169 (36 %)	19 (41 %)
Anthracycline-based chemotherapy					
No	407 (79 %)	373 (79 %)	34 (79 %)	373 (80 %)	34 (74 %)
Yes	107 (21 %)	98 (21 %)	9 (21 %)	95 (20 %)	12 (26 %)
Topoisomerase-based chemotherapy					
No	458 (89 %)	426 (90 %)	32 (74 %)	414 (88 %)	44 (96 %)
Yes	56 (11 %)	45 (10 %)	11 (26 %)	54 (12 %)	2 (4 %)
High-risk antimetabolites					
No	372 (72 %)	351 (75 %)	21 (49 %)	340 (73 %)	32 (70 %)
Yes	142 (28 %)	120 (25 %)	22 (51 %)	128 (27 %)	14 (30 %)
ABO gene					

Variable	Overall (N=514)	VTE		Clinically Relevant Bleeding	
		No (N=471)	Yes (N=43)	No (N=468)	Yes (N=46)
Non-O blood type	315 (61 %)	283 (60 %)	32 (74 %)	286 (61 %)	29 (63 %)
O blood type	199 (39 %)	188 (40 %)	11 (26 %)	182 (39 %)	17 (37 %)
F5 gene, FVL					
Mutated	21 (4 %)	14 (3 %)	7 (16 %)	20 (4 %)	1 (2 %)
Normal	493 (96 %)	457 (97 %)	36 (84 %)	448 (96 %)	45 (98 %)
F13 gene					
Mutated	219 (43 %)	203 (43 %)	16 (37 %)	199 (43 %)	20 (43 %)
Normal	295 (57 %)	268 (57 %)	27 (63 %)	269 (57 %)	26 (57 %)
F5 gene, K858R					
Mutated	236 (46 %)	219 (46 %)	17 (40 %)	217 (46 %)	19 (41 %)
Normal	278 (54 %)	252 (54 %)	26 (60 %)	251 (54 %)	27 (59 %)
FGG gene					
Mutated	204 (40 %)	189 (40 %)	15 (35 %)	181 (39 %)	23 (50 %)
Normal	310 (60 %)	282 (60 %)	28 (65 %)	287 (61 %)	23 (50 %)
F11 gene					
Mutated	392 (76 %)	356 (76 %)	36 (84 %)	352 (75 %)	40 (87 %)
Normal	122 (24 %)	115 (24 %)	7 (16 %)	116 (25 %)	6 (13 %)
F2 gene, Prothrombin G20210A					
Mutated	10 (2 %)	9 (2 %)	1 (2 %)	10 (2 %)	0 (0 %)
Normal	504 (98 %)	462 (98 %)	42 (98 %)	458 (98 %)	46 (100 %)
Platelet Count[b], mean (SD)	-0.03 (± 1.01)	-0.03 (± 1.02)	-0.02 (± 0.96)	-0.05 (± 1.01)	0.17 (± 1.06)

Variable	Overall (N=514)	VTE		Clinically Relevant Bleeding	
		No (N=471)	Yes (N=43)	No (N=468)	Yes (N=46)
Hemoglobin[a], mean (SD)	-0.02 (± 1.00)	-0.02 (± 0.97)	0.04 (± 1.34)	0.01 (± 1.01)	-0.35 (± 0.88)
While Blood Count[b], mean (SD)	-0.01 (± 1.00)	-0.0006 (± 1.05)	-0.14 (± 0.78)	-0.02 (± 1.02)	0.10 (± 1.13)
CrCl[b], mean (SD)	0.02 (± 0.99)	0.01 (± 1.00)	0.04 (± 0.87)	0.02 (± 0.98)	0.005 (± 1.10)
CLT[b], mean (SD)	0.02 (± 1.02)	0.02 (± 1.03)	-0.06 (± 0.91)	0.003 (± 1.02)	0.14 (± 1.01)
FXIa-C1[b], mean (SD)	-0.0008 (± 1.01)	-0.002 (± 1.01)	0.009 (± 1.00)	-0.004 (± 1.01)	0.03 (± 0.98)
aPAI-1[b], mean (SD)	0.003 (± 1.01)	0.02 (± 1.02)	-0.14 (± 0.89)	0.01 (± 1.02)	-0.07(± 0.92)
sP-selectin[b], mean (SD)	-0.00005 (± 1.01)	0.01 (± 0.97)	-0.11 (± 1.39)	0.006 (± 0.97)	-0.06 (± 1.33)
D-dimer[b], mean (SD)	-0.002 (± 1.01)	-0.03 (± 0.99)	0.30 (± 1.14)	-0.02 (± 1.00)	0.25 (± 1.06)
CRP[b], mean (SD)	-0.008 (± 1.00)	-0.02 (± 0.99)	0.12 (± 1.05)	-0.05 (± 0.99)	0.40 (± 1.00)
HGH[b], mean (SD)	0.011 (± 1.00)	-0.01 (± 1.00)	0.12 (± 1.05)	-0.009 (± 1.00)	0.22 (± 1.07)
NT-proBNP[b], mean (SD)	-0.005 (± 1.00)	-0.01 (± 1.00)	0.04 (± 1.01)	-0.03 (± 0.97)	0.23 (± 1.22)
hs-TnT[b], mean (SD)	-0.02 (± 0.98)	-0.04 (± 0.94)	0.20 (± 1.36)	-0.03 (± 0.98)	0.03 (± 1.00)
TSH[b], mean (SD)	-0.003 (± 0.98)	-0.01 (± 1.00)	0.08 (± 0.80)	-0.02 (± 0.97)	0.21 (± 1.08)

Variable	Overall (N=514)	VTE		Clinically Relevant Bleeding	
		No (N=471)	Yes (N=43)	No (N=468)	Yes (N=46)
GDF-15[b], mean (SD)	-0.01 (± 1.01)	-0.03 (± 1.01)	0.21 (± 0.99)	-0.02 (± 0.99)	0.07 (± 1.14)
CXCL-12[a], mean (SD)	-0.003 (± 1.01)	-0.004 (± 1.02)	0.009 (± 0.90)	-0.03 (± 1.01)	0.30 (± 1.02)
microparticles[b], mean (SD)	-0.02 (± 1.05)	-0.05 (± 1.08)	0.31 (± 0.65)	-0.01 (± 1.02)	-0.66 (± 1.32)

[a] standardized only

[b] log-transformed and standardized

Supplemental Table 2. Variable definitions

Parameter	**Description**
Sex	Categorized as 1 for females and 0 for males (reference).
Age	Standardized.
BMI	Log-transformed and standardized.
Previous VTE	Categorized as 1 when patient was diagnosed with a previous DVT or PE and 0 when not diagnosed with previous DVT or PE.
Apixaban	Categorized as 1 when randomized to receiving apixaban (2.5mg bid po) vs 0 when randomized to receiving placebo.
Cancer Type and Stage	Categorized using two dummy variables: - "Hematological": categorized as 1 when patient was diagnosed with Lymphoma, Myeloma or Leukemia and 0 when diagnosed with other types of cancer. - "Advanced Solid": categorized as 1 when patient was diagnosed with Stage 3 or 4 solid cancer, and 0 when diagnosed with hematological or Stage 1 or 2 solid cancer.
Platinum-based chemotherapy	Categorized as 1 when patient received cisplatin, carboplatin or oxaliplatin chemotherapy and 0 when none of these chemotherapies were part of their regimen.
Taxane-based chemotherapy	Categorized as 1 when patient received docetaxel or paclitaxel chemotherapy and 0 when none of these chemotherapies were part of their regimen.
Anthracyclines-based chemotherapy	Categorized as 1 when patient received doxorubicin or epirubicin chemotherapy and 0 when none of these chemotherapies were part of their regimen.
Topoismerase inhibitor chemotherapy	Categorized as 1 when patient received irinotecan, topotecan or etoposide chemotherapy and 0 when none of these chemotherapies were part of their regimen.

High-risk antimetabolites	Categorized as 1 when patient received capecitabine, fluorouracil or gemcitabine chemotherapy and 0 when none of these chemotherapies were part of their regimen.
Platelet Count	Log-transformed and standardized.
Hemoglobin	standardized.
White Blood Count	Log-transformed and standardized.
Creatinine clearance	Log-transformed and standardized.
Activated factor XIa-C1 inhibitor complex (FXIa-C1)	Log-transformed and standardized. Measured using an in-house sandwich ELISA. (Ilich et al 2020)
Plasminogen activator-inhibitor-1 (PAI-1)	Log-transformed and standardized. Measured by ELISA (Molecular Innovations, Novi, MI, USA, cat. no. HPAIKT). (Ilich et al 2020)
soluble P-selectin (sP-selectin)	Log-transformed and standardized. Measured using a commercially available ELISA (Human P-selectin/CD62P Quantikine, R&D Systems, Minneapolis, MN, USA; cat#DPSE00) (Shaw et al 2020)
D-dimer	Log-transformed and standardized. Measured using an immunoturbidimetric assay (STA-Liatest D-Di 20; Diagnostica Stago, Asnières, France). (Shaw et al 2020)
C-reactive protein (CRP)	Log-transformed and standardized. Measured using a particle-enhanced immunoturbidimetric assay on Roche cobas 6000 automated chemistry analyzer. (Not yet published)
Human Growth Hormone (HGH)	Log-transformed and standardized. Measured using an electrochemiluminescence immunoassay on Roche cobas 6000 automated chemistry analyzer.
N-terminal pro-B-type natriuretic peptide (NT-proBNP)	Log-transformed and standardized. Measured using electrochemiluminescence immunoassays on Roche cobas 6000 automated chemistry analyzer.
high-sensitivity Troponin T (hs-TnT)	Log-transformed and standardized. Measured using an electrochemiluminescence immunoassay on Roche cobas 6000 automated chemistry analyzer.

Thyroid stimulating hormone (TSH)	Log-transformed and standardized. Measured using an electrochemiluminescence immunoassay on Roche cobas 6000 automated chemistry analyzer.
Growth differentiation factor (GDF-15)	Log-transformed and standardized. Measured using an ELISA immunoassay (Biotechne Quantikine GDF-15, R&D systems) on Roche cobas 6000 automated chemistry analyzer.
CXC motif chemokine ligand 12 (CXCL-12)	Standardized. Measured using ELISA (Biotechne, R&D Systems).
EV pro-coagulant activity	Log-transformed and standardized. Measured using a commercially available assay, Zymuphen EV Pro-coagulant activity assay.
ABO blood type (rs8176719)	Categorized as 1 when patient had a non-O blood type (i.e., A, B or AB) and 0 when patient had a O blood type. Identified using the Agena Bioscience iPlex method (Agena Bioscience, San Diego, CA, USA) according to the manufacturer's instructions. (Roy et al 2022)
Factor V Leiden gene (rs6025)	Categorized as 1 when patient had heterozygous or homozygous FVL mutation and 0 when patient had wild-type. Identified using the Agena Bioscience iPlex method (Agena Bioscience, San Diego, CA, USA) according to the manufacturer's instructions. (Roy et al 2022)
F13 gene (rs5985)	Categorized as 1 when patient had heterozygous or homozygous F13 mutation and 0 when patient had wild-type. Identified using the Agena Bioscience iPlex method (Agena Bioscience, San Diego, CA, USA) according to the manufacturer's instructions. (Roy et al 2022)
F5 K858R gene (rs4524)	Categorized as 1 when patient had heterozygous or homozygous F5 mutation and 0 when patient had wild-type. Identified using the Agena Bioscience iPlex method (Agena Bioscience, San Diego, CA, USA) according to the manufacturer's instructions. (Roy et al 2022)
FGG gene (rs2066865)	Categorized as 1 when patient had heterozygous or homozygous FGG mutation and 0 when patient had wild-type. Identified using the Agena Bioscience iPlex method (Agena Bioscience, San Diego, CA, USA) according to the manufacturer's instructions. (Roy et al 2022)

F11 gene (rs2036914)	Categorized as 1 when patient had heterozygous or homozygous F11 mutation and 0 when patient had wild-type. Identified using the Agena Bioscience iPlex method (Agena Bioscience, San Diego, CA, USA) according to the manufacturer's instructions. (Roy et al 2022)
Prothrombin G20210A gene (rs1799963)	Categorized as 1 when patient had heterozygous or homozygous F2 mutation and 0 when patient had wild-type. Identified using the Agena Bioscience iPlex method (Agena Bioscience, San Diego, CA, USA) according to the manufacturer's instructions. (Roy et al 2022)

Supplemental Table 3. Accuracy measures of XGBoost models when using a sensitivity of 80%

Outcome	Model	Pred % Threshold	Sensitivity*	Specificity	NPV	PPV
VTE	XGBoost (Model A)	0.16	0.80 (0.64-0.90)	0.93 (0.90-0.95)	0.98 (0.96-0.99)	0.51 (0.38-0.63)
	XGBoost (Model B)	NA				
Bleeding	XGBoost (Model A)	0.13	0.80 (0.66-0.91)	0.90 (0.87-0.93)	0.98 (0.96-0.99)	0.45 (0.34-0.57)
	XGBoost (Model B)	0.12	0.80 (0.66-0.91)	0.84 (0.80-0.87)	0.98 (0.96-0.99)	0.32 (0.24-0.42)

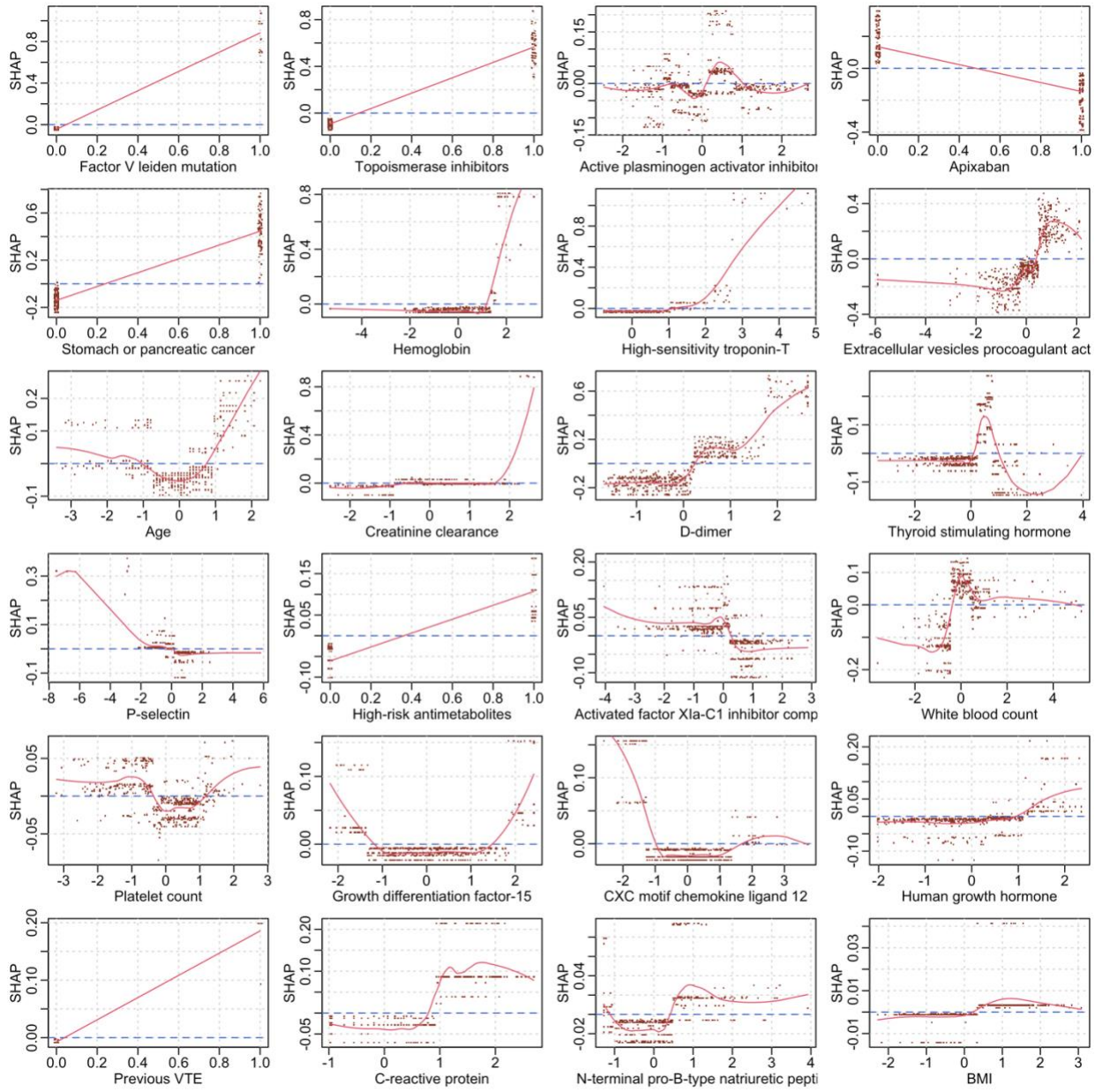
*~80%

Supplemental Table 4. Sensitivity analysis of performance measures using a second imputed dataset

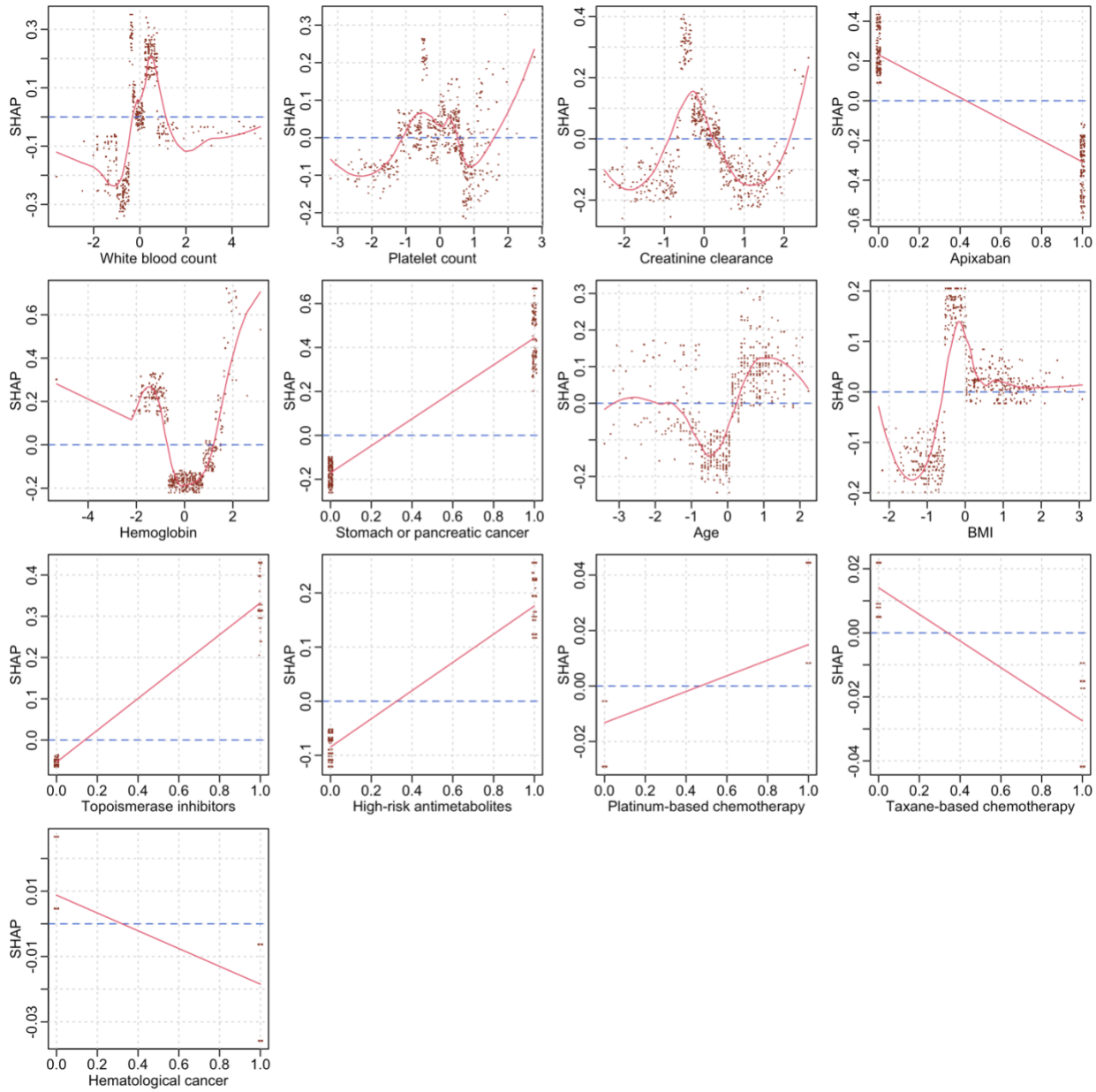
Model	LASSO	XGBoost (Model A)	XGBoost (Model B)
VTE			
AUROC	0.72 (0.63-0.79)	0.92 (0.88-0.96)	0.85 (0.81-0.88)
PRAUC	0.17 (0.07-0.30)	0.74 (0.58-0.83)	0.32 (0.14-0.45)
Log loss	0.27 (0.22-0.33)	0.23 (0.19-0.26)	0.27 (0.23-0.31)
Brier score	0.07 (0.06-0.09)	0.06 (0.05-0.08)	0.08 (0.06-0.10)
Clinically Relevant Bleeding			
AUROC	0.60 (0.52-0.68)	0.88 (0.84-0.91)	0.86 (0.82-0.90)
PRAUC	0.06 (0.01-0.14)	0.59 (0.43-0.69)	0.50 (0.33-0.60)
Log loss	0.31 (0.25-0.37)	0.27 (0.24-0.31)	0.26 (0.22-0.30)
Brier score	0.08 (0.07-0.11)	0.08 (0.07-0.10)	0.08 (0.06-0.09)

AUROC= Area under the receiver operating characteristic (ROC) curve; PRAUC= Precision-recall ROC curve

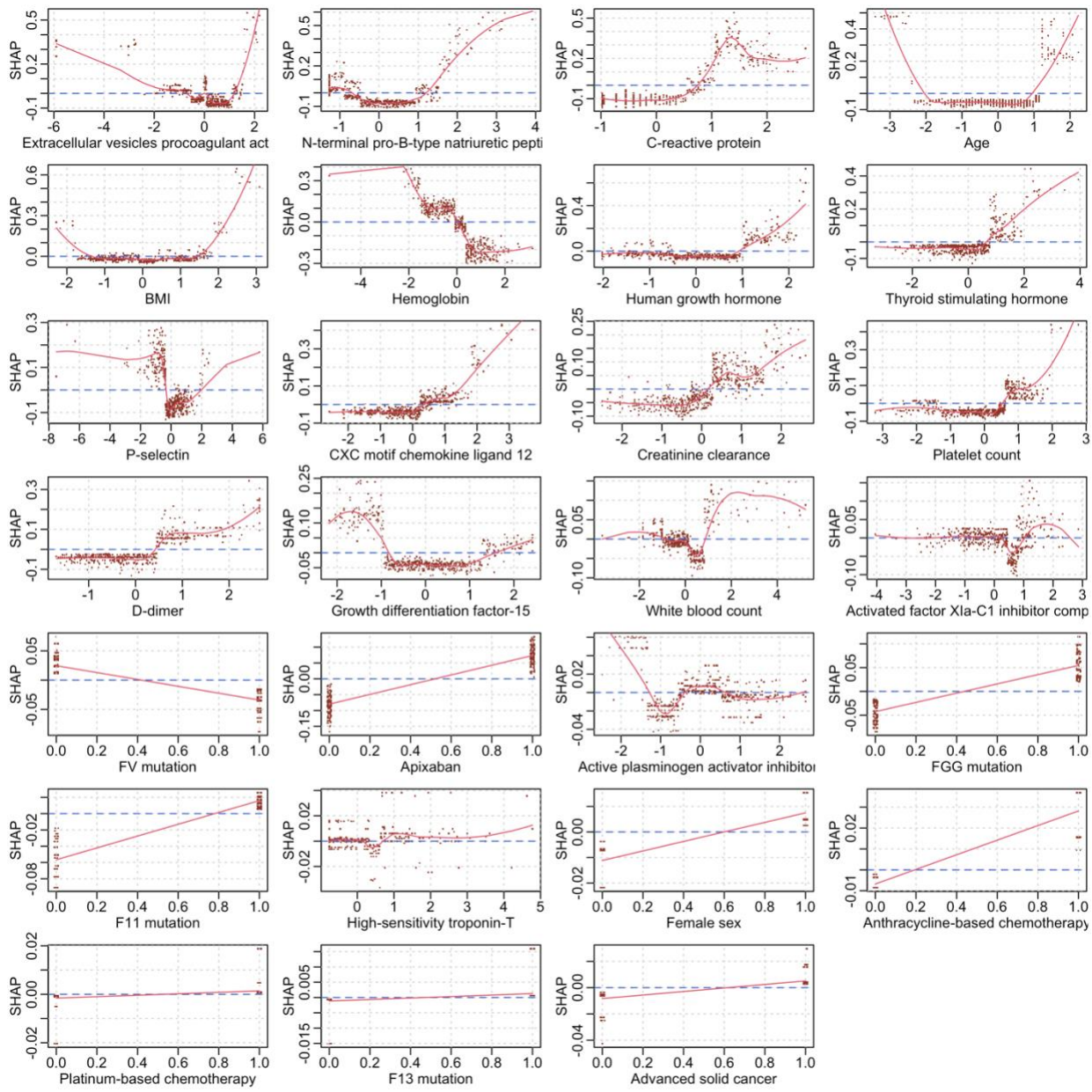
Model - A = all baseline variables; Model – B = only variables measured during standard clinical practice



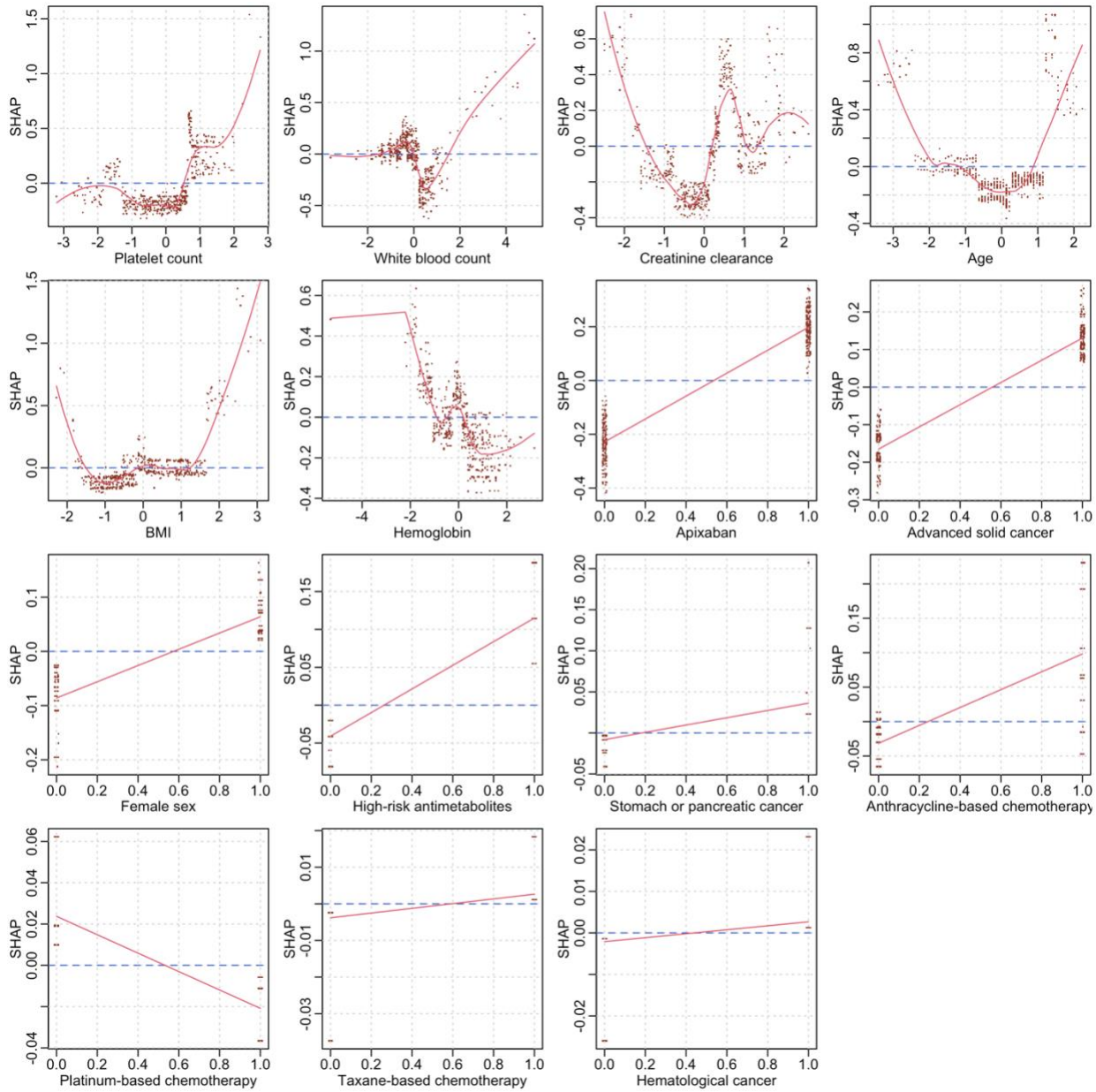
Supplemental Figure 1. SHapley Additive exPlanations (SHAP) values for predictors included in the VTE XGBoost model A



Supplemental Figure 2. SHapley Additive exPlanations (SHAP) values for predictors included in the VTE XGBoost model B



Supplemental Figure 3. SHapley Additive exPlanations (SHAP) values for predictors included in the bleeding XGBoost model A



Supplemental Figure 4. SHapley Additive exPlanations (SHAP) values for predictors included in the bleeding XGBoost model B

Chapter 7

Discussion

The central aim of this doctoral thesis is to fill important evidence gaps relating to VTE and bleeding risk stratification in ambulatory patients with cancer, in hopes of improving their prediction and management. In Chapter 1, I reviewed the epidemiology and current primary prevention strategies for cancer-associated VTE and summarized the clinical dilemma and current evidence gaps relating to risk stratification in ambulatory patients with cancer. Chapter 2 and 3 aimed to fill the first gap by summarizing and investigating the association between genetic risk factors and VTE in cancer patients. Chapter 4 presented a systematic review and meta-analysis synthesizing current evidence on biomarkers for VTE risk assessment in cancer patients. In Chapter 5, the association between inflammatory and cardiac biomarkers, and VTE and bleeding risk was investigated. With the genetic factors from Chapter 2, the inflammatory and cardiac biomarkers from Chapter 5 and other variables, in Chapter 6, machine learning models for the prediction of VTE and bleeding risks in ambulatory cancer patients were developed. Lastly, in this final chapter, the key findings, clinical implications, strengths and limitations of this doctoral thesis will be discussed.

7.1 Summary of key findings

Impact of inherited thrombophilia on VTE and bleeding risk in cancer – In the first two studies of this thesis (Chapter 2 and 3), the role of inherited thrombophilia on the risk of cancer-associated VTE and bleeding was assessed. We evaluated the risk of VTE and bleeding in ambulatory intermediate-to-high risk patients (Khorana score ≥2) starting chemotherapy (Chapter 2) and conducted a systematic review and meta-analysis of studies investigating the risk of VTE in cancer patients with inherited thrombophilia (Chapter 3). We found that the risk of VTE was increased in cancer patients with non-O blood types (i.e., A, B or AB) compared to O blood types, and in patients with heterozygous and homozygous Factor V Leiden (FVL) and Prothrombin Factor II G20210A mutations compared to cancer patients without these mutations. Specifically, in our secondary analysis of ambulatory intermediate-to-high risk cancer patients, the risk of VTE was 2.72-, 5.2- and 1.36-fold higher in those with non-O blood types, FVL and

Prothrombin Factor II G20210A mutations, respectively. Similarly, our meta-analysis confirmed significantly higher risks of VTE among cancer patients with non-O blood types [Odds Ratio: 1.56 (95%CI: 1.28-1.90)], FVL [Odds Ratio: 2.28 (95%CI: 1.51-3.48)] and Prothrombin Factor II G20210A [Odds Ratio: 2.14 (95%CI: 1.14-4.03)] mutations compared to cancer patients without these thrombophilia. In Chapter 2, we further investigated the benefit versus harm of thromboprophylaxis in ambulatory cancer patients with inherited thrombophilia. The results showed the effectiveness of prophylactic anticoagulation use in patients with FVL and non-O blood types in reducing the rate of VTE [Absolute Risk Reduction: 119.48 person-years (95%CI: 23.88-246.28) and 28.38 person-years (95%CI: 13.52-42.24), respectively] without significantly increasing the risk of bleeding (Absolute Risk Increase: no events and 6.82 (95%CI: -9.45-23.08), respectively). Collectively, these two studies provide evidence that non-O blood types, FVL and Prothrombin Factor II G20210A mutations are important genetic risk factors for VTE and thromboprophylaxis in ambulatory cancer patients with these inherited thrombophilia may be considered.

Association between biomarkers and VTE and bleeding risk in cancer patients – In the third and fourth studies of this thesis, we conducted a systematic review and meta-analysis synthesizing current evidence on blood biomarkers analyzed as VTE predictors in cancer patients (Chapter 4) and investigated novel blood biomarkers (i.e., C-reactive protein [CRP], growth differentiation factor-15 [GDF-15], N-terminal pro-B-type natriuretic peptide [NT-proBNP] and high-sensitivity Troponin T [hs-TnT]) in relation to VTE and bleeding risk in ambulatory cancer patients starting chemotherapy (Chapter 5). In the systematic review and meta-analysis (Chapter 4), nine candidate blood biomarkers were identified as potential predictors that may help in optimizing VTE prediction in cancer patients, which differed based timing of measurement (i.e., at cancer diagnosis, prechemotherapy and preoperative). We identified four biomarkers at cancer diagnosis (factor VIII, time to peak thrombin, hemoglobin <100g/L and white blood count >11 x 10^9/L), three biomarkers pre-chemotherapy (d-dimer, fibrinogen, mean platelet volume, neutrophil-lymphocyte ratio >3), and one biomarker preoperatively (platelet count or platelet count>400 x 10^9/L) that were associated with VTE risk in cancer patients. In Chapter 5, multivariate analyses showed that higher GDF-15 at baseline was associated with an increased VTE risk but not bleeding. Meanwhile, higher baseline NT-proBNP and CRP levels were

associated with an increased bleeding risk, but not VTE. Additionally, the results also suggest that an increase in hs-TnT levels from baseline to month-1 and an increase in CRP levels from baseline to month-3 were associated with an increased 7-month risk of VTE, but not bleeding. All in all, Chapter 4 and Chapter 5 provided insight on the use of biomarkers for VTE and bleeding risk prediction in cancer patients, more targeted towards ambulatory patients. Chapter 5 further suggests that there may be an interplay between inflammation, cardiac function and coagulability, reflected by inflammatory and cardiac biomarkers.

Machine learning for predicting the risk of VTE and bleeding in ambulatory cancer patients – In the final component of this thesis presented in Chapter 6, we developed machine learning models for predicting the risk of VTE and bleeding in ambulatory cancer patients. In the models, we included the previously assessed inherited thrombophilia from Chapter 2 and 3, most of the evidence-based blood biomarkers from Chapter 4, the novel biomarkers from Chapter 5 and important clinical risk factors such as age, body mass index, stage and type of cancer, etc. Three models were developed for both VTE and bleeding, one of which used logistic regression with L1 regularization (also known as least absolute shrinkage and selection operator [LASSO]), and two others using the XGBoost machine learning algorithm. One of the XGBoost models included all potential variables and the other included only routinely measured variables. We found that XGBoost models including all potential variables (i.e., biomarkers and inherited thrombophilia) had the highest discriminatory performance - higher than existing risk assessment models. This suggests that some genetic and biomarkers, which are not collected routinely, may help with prediction and thus, may be important predictors to consider when performing VTE or bleeding risk assessment in ambulatory cancer patients. In particular, FVL, hs-TnT, active plasminogen activator inhibitor-1 (PAI-1), extracellular vesicles (EV)-proacoagulant activity and d-dimer may be important VTE risk predictors whereas EV-procoagulant activity, NT-proBNP, CRP and d-dimer may be important bleeding risk predictors to consider. Additionally, the machine learning models developed in this Chapter, may have clinical implications to determine the risks of VTE and bleeding in an ambulatory cancer patient, but they require further validation.

7.2 Implications for clinical practice

In ambulatory cancer patients, current guidelines suggest thromboprophylaxis with apixaban, rivaroxaban or LMWH in those with high risk for at least 6-months.[1–6] This suggestion stems from the results of randomized clinical trials, two of which used a validated risk score (i.e., Khorana score ≥ 2) to identify higher risk cancer patients who could benefit from thromboprophylaxis.[7–11] However, with the limited uptake of VTE risk assessment and thromboprophylaxis in ambulatory cancer patients in clinical practice,[12,13] there remains a critical gap between evidence-based recommendations and real-world implementation, highlighting the need for improved strategies to identify and manage high-risk patients.

The findings from Chapters 2 and 3 demonstrate that inherited thrombophilia including ABO blood type, FVL and Prothrombin Factor II G20210A mutations are important genetic risk factors contributing to thrombotic risk and that thromboprophylaxis effectively reduces this risk in patients with non-O blood types and FVL without significantly increasing the risk of bleeding. Together, these results support the consideration of non-O blood types, FVL and Prothrombin Factor II G20210A as additional risk factors that clinicians can use to identify ambulatory cancer patients most likely to benefit from primary prevention therapy, given that currently, inherited thrombophilia screening is not included in clinical guidelines. As such, at present, these results have clinical implications potentially for routine screening, but certainly for informing individualized risk stratification and guiding thromboprophylaxis decisions in patients who are known to have these genetic risk factors. Unlike FVL and Prothrombin Factor II G20210A mutations, which require specialized genetic testing, ABO blood is often already documented or can be easily and inexpensively determined via blood typing. Further research evaluating clinical utility and cost-effectiveness may facilitate integration into practice. Broader implications, such as psychological, social and economic consequences of test results must also be considered. Until these issues are studied, routine screening for inherited thrombophilia in cancer patients is unlikely to become standard of care. However, our results support the consideration of primary thromboprophylaxis in patients with a known inherited thrombophilia.

In addition to genetic predisposition, cancer-associated VTE is also influenced by the direct prothrombotic effects of cancer and its treatments (e.g., chemotherapy), which collectively disrupt coagulation, inflammatory and hemostatic pathways. Consequently, cancer patients who develop thrombotic or bleeding complications often exhibit different biomarker profiles

compared to those who do not. Findings from Chapters 4 to 6 of this thesis highlight several circulating blood biomarkers (e.g., factor VIII, time to peak thrombin, hemoglobin, white blood count, fibrinogen, mean platelet volume, neutrophil-lymphocyte ratio, platelet count, GDF-15, CRP, NT-proBNP, hs-TnT, etc.) that may help identify high-risk ambulatory cancer patients. If confirmed through external validation and implementation studies, these biomarkers could support more personalized risk stratification and guide thromboprophylaxis decisions in ambulatory cancer patients. However, demonstrating an association between biomarker levels and VTE or bleeding risk alone is not sufficient to justify clinical implementation. There are multiple phases and barriers that must be addressed for biomarker implementation in clinical practice. As outlined by Shaw et al[14], the phases leading to the use of a VTE biomarker in clinical practice include initial laboratory discovery (Phase 1), assay standardization and validation (Phase 2), retrospective clinical association (Phase 3), prospective clinical association (Phase 4) and evaluation of clinical effectiveness and disease control through randomized controlled trials (Phase 5). Given that Chapters 4 and 5 primarily focus on unadjusted associations and previously collected data, respectively, two critical phases remain to confirm the clinical utility of the proposed biomarkers: prospective validation and randomized controlled trials to evaluate their impact in real-world clinical practice. Additionally, given that some of the identified blood biomarkers are not routinely measured, further evaluation of their cost-effectiveness and feasibility is needed before they can be integrated into routine VTE or bleeding risk assessment in ambulatory cancer patients.

Moreover, the significant associations observed between inflammatory and cardiac biomarkers and coagulation in Chapters 4 to 6 suggest that clinicians should adopt a broader perspective when assessing VTE and bleeding risk in cancer patients. This entails considering not only coagulation pathways but also upstream factors or predisposing conditions such as systemic inflammation and cardiac dysfunction. Currently, most, if not all, existing VTE risk assessment tools focus primarily on traditional coagulation risk factors, with limited integration of these broader physiological contributors. For example, while the Khorana score and its derivatives (i.e., Protecht, Conko, Onkotev scores) as well as the COMPASS-CAT score include complete blood count components, only the Vienna CATS score and CATS/MICA nomogram integrate additional procoagulant biomarkers (i.e., d-dimer, soluble P-selectin), with none including broader biomarkers related to other predisposing conditions.[15–21] Similarly, although

some bleeding scores (e.g., ABC-bleeding score, CAT-Bleed score) incorporate broader physiological biomarkers such as, hs-TnT, GDF-15 and creatinine clearance, they remain limited to the patient population in which they were developed. Consequently, there is a clear gap in the multidimensionality, generalizability and applicability of existing risk models. Our findings in Chapter 6 further support the value of a more integrative approach, as inflammatory and cardiac biomarkers and other upstream biomarkers, emerged as top predictors in our risk models. Incorporating such upstream factors may enhance the predictive accuracy of existing tools and better reflect the complex pathophysiology underlying cancer-associated thrombosis and bleeding.

The identification of distinct biomarkers at different clinical time points (i.e., preoperatively, prechemotherapy and at cancer diagnosis) presented in Chapter 4 and longitudinal changes in biomarker levels presented in Chapter 5, also have important implications for clinical practice. These findings suggest that the risk of VTE in cancer patients is not static and evolves over the course of the disease and in response to therapeutic interventions. Current studies support these findings, demonstrating that VTE and bleeding risk is heterogenous and influenced by multiple time-varying factors, including cancer stage, treatment modality and medical history or comorbidities.[22–24] This is very well illustrated in *Cancer-associated Thrombosis: new findings in translation science, prevention and treatment* book[25], Chapter 12 (page 171)[26], which includes a plot demonstrating the changes in VTE risk over the natural course of malignant disease. The plot shows that the risk increases rapidly after cancer diagnosis, with potential hospitalization and chemotherapy treatment, and decreases after remission. As such, integrating time-specific biomarker assessments or dynamic risk stratification using biomarkers such as the proposed biomarkers in Chapter 5, could enable more tailored decision-making regarding thromboprophylaxis in ambulatory cancer patients. Particularly, it may help monitor any changes in risk while on chemotherapy or anticoagulation therapy, as seen in this Chapter. Additionally, our findings of inconsistent associations between biomarker levels and VTE outcomes at different clinical time points in Chapter 4 also highlighted that biomarker levels may vary in response to therapeutic interventions like chemotherapy, which can limit their predictive power at different time points. For instance, in our meta-analyses of blood counts in Chapter 4, we found that hemoglobin levels below 100g/L and white blood counts over $11x10^9$/L were associated with VTE risk at cancer diagnosis but not

prechemotherapy, likely due to the effects of earlier chemotherapy cycles on these parameters.[27–29] This underscores the need to carefully consider the timing of biomarker assessments and their applicability in clinical decision-making.

The limitations of current VTE risk prediction models have led to growing recognition that improving these models, or developing new ones, could improve thromboprophylaxis decision-making and patient outcomes. Notably, no specific bleeding risk model has been successfully developed for ambulatory cancer patients to aid with bleeding risk stratification. To improve these evidence gaps, Chapter 6 presents the development of highly discriminatory machine learning models to predict both VTE and bleeding in ambulatory cancer patients. Although these models were trained in a relatively modest cohort of cancer patients, they demonstrate promising performance and offer potential for clinical application. By integrating diverse and high-dimensional data, such as biomarkers, genetic risk factors and clinical characteristics, these models may offer a more nuanced and individualized risk assessments than traditional risk scores. With further external validation and refinement, these models could support more precise identification of patients most likely to benefit the most from thromboprophylaxis. Moreover, since current guidelines do not recommend a formal bleeding risk assessment tool in ambulatory cancer patients due to a lack of evidence, the development of a validated accurate bleeding risk model in these patients, such as that proposed in Chapter 6, could also eventually lead to future guideline updates. Importantly, the simultaneous use of both VTE and bleeding risk models could support a more balanced and evidenced-informed approach to thromboprophylaxis decisions, minimizing both under-treatment and overtreatment in this patient population.

7.3 Implications for future research

The findings presented in this thesis highlight several important directions for future research aimed at improving risk prediction and clinical management of VTE and bleeding in ambulatory cancer patients. The potential role of inherited thrombophilia screening in cancer requires further investigation. To justify inherited thrombophilia screening in clinical practice, future studies must demonstrate that inherited thrombophilia screening offers substantial improvement in prognostic accuracy beyond existing risk factors, while also providing a clear net clinical benefit. This includes demonstrating that the advantages of screening outweigh potential harms, such as

the psychological and economic impact of a positive test, which could lead to overtreatment or undertreatment and negatively impact quality of life. Cost-effectiveness analyses will also be essential to determine the practicality of incorporating inherited thrombophilia screening into clinical oncology practice. Thus, our findings of an increased VTE risk in patients with select inherited thrombophilia (Chapters 2 and 3) has sparked a range of new research questions and opportunities for future research.

Furthermore, the associations between biomarkers and VTE risk (Chapter 4), as well as between inflammatory and cardiac biomarkers and both VTE and bleeding risk (Chapter 5), warrant validation in larger, independent cohorts to confirm their clinical relevance. In particular, prospective validation in a large cohort of cancer patients with different cancer types, alongside evaluation in randomized controlled trials, is necessary to establish generalizability, feasibility and utility of these biomarkers in clinical practice. Thus, clinicians or researchers may seek to externally validate our findings in other cancer cohorts. The results from Chapter 4 may also help future researchers determine which biomarkers to investigate further compared to which ones should not be. Additionally, since little is known about the exact mechanistic link between inflammatory and cardiac biomarkers and VTE or bleeding risk, future research should aim to elucidate the biological mechanisms linking these biomarkers to hyper- or hypo-coagulability. Moreover, our findings of increased VTE and bleeding risk among cancer patients with specific inflammatory or cardiac biomarker profiles in Chapter 5 and their added prediction in Chapter 6 may prompt researchers to explore additional biomarkers associated with other upstream factors or predisposing conditions, in order to expand on and better capture the multifactorial nature of cancer-associated VTE. Examples may be biomarkers associated with diabetes, another predisposing condition for VTE[30], or biomarkers which promote the expression of cell adhesion molecules (i.e., interleukin-1β) [31], another potential upstream factor contributing to clot formation.

The identification of distinct biomarkers at different clinical time points (i.e., preoperatively, prechemotherapy and at cancer diagnosis) presented in Chapter 4 and longitudinal changes in biomarker levels presented in Chapter 5 highlights the potential usefulness of dynamic risk assessment models. Future studies should therefore prioritize the development and validation of dynamic VTE and bleeding risk assessments models and assess whether they perform better than static models. Recent work by Lee et al[32] has shown promising

results in this area. The authors demonstrated that incorporating time-updated biomarker levels into predictive models significantly improved the accuracy of VTE risk stratification in cancer patients compared to static baseline models. The longitudinal changes in inflammatory and cardiac biomarkers presented in Chapter 5 may be valuable predictors to include in future dynamic models. In addition, the different biomarkers associated with VTE events at different clinical time points in Chapter 4 may help guide the development of dynamic risk models, given that they might reflect temporally varying biological processes and offer predictive value that is specific to certain stages in the course of malignant disease.

Finally, while the machine learning models developed in this thesis (Chapter 6) showed promising discriminatory performance, further refinement and validation are necessary to ensure their generalizability and utility across diverse cancer populations. Particularly, future search should explore generalizability of our proposed machine learning models in patients with Khorana scores below 2 and in cancer types underrepresented in the current cohort, such as hematological malignancies and breast cancer. Prospective validation and implementation studies will be crucial to confirm generalizability of our proposed machine learning models (Chapter 6) and assess their integration into clinical practice and impact on patient care, respectively.

7.4 Strengths and limitations

While this thesis offers valuable insights, its findings should be interpreted with consideration of both its strengths and limitations. First, for the studies examining associations (Chapters 2 and 5), residual confounding bias may be present, as the relatively small sample size limited our ability to adjust for all potential confounders. However, to limit this bias as much as possible, we carefully selected and adjusted the analyses for the most important clinically relevant and evidence-based confounders. Second, in our meta-analyses (Chapters 3 and 4), confounding is also a potential limitation, as pooled estimates were unadjusted. But this approach was chosen deliberately due to substantial heterogeneity in adjustment strategies across studies, many of which employed potentially biased or unclear adjustment strategies (e.g., not determined a priori, lack of explanation, adjusting for non-confounders, or overadjustment), which could have introduced greater bias than using unadjusted estimates. Third, the associations involving biomarkers observed in our meta-analysis (Chapter 4) and cohort of cancer patients (Chapter 5)

should be interpreted cautiously, as they are either novel, based on unadjusted pooled estimates, or have yet to be validated in an independent cohort of cancer patients. Furthermore, the cohort of cancer patients from Chapter 5 included patients with an intermediate to high risk of VTE based on a Khorana score of ≥2, limiting generalizability. Therefore, further studies are needed to replicate, generalize and adjust these associations in larger, other well-controlled cohorts of patients with cancer. Fourth, many AVERT trial patients (approximately 36%) randomized to apixaban permanently or temporary discontinued treatment prior to the end of the trial. As such, the subgroup sensitivity analyses that were performed in Chapter 5 in patients randomized to the apixaban group (i.e., association between biomarkers and clinically relevant bleeding risk in patients randomized to apixaban) and strength of apixaban as a predictor of reduced VTE risk (Chapter 6) could be biased. Specifically, these results could be biased toward the null (i.e., underestimated) because treatment discontinuation reduces actual exposure to apixaban, thereby attenuating both its harmful and beneficial effects. To address this limitation in Chapter 2, when investigating the rate reduction in VTE and rate increase in clinically relevant bleeding according to inherited thrombophilia status, we stratified incidence rates according to time on and off anticoagulation, allowing for a more accurate assessment of event rates by actual anticoagulant exposure time. Fifth, our machine learning models, developed to predict VTE and bleeding, were not externally validated, raising the potential for overfitting. Nevertheless, we sought to minimize this risk through rigorous internal validation and careful hyperparameter tuning using cross-validation during model development.

Despite these limitations, this thesis also has notable strengths. Most importantly, the consistency, strength, and biological plausibility of the genetic associations observed across our independent cancer cohort (Chapter 2) and meta-analysis (Chapter 3) supported the validity of the findings on inherited thrombophilia, particularly non-O blood type, FVL and Prothrombin Factor II G20210A, as important risk factors for cancer-associated VTE. Additionally, one key strength is that we examined the intersection of inherited thrombophilia and anticoagulation use—an area that, to our knowledge, has not been previously addressed in this population, offering a novel contribution to the field. Moreover, the use of multiple, complementary methodologies, including cohort analyses to assess real-world associations (Chapters 2 and 5), meta-analyses to synthesize existing evidence (Chapters 3 and 4), and machine learning to develop predictive models (Chapter 6), strengthens the thesis by providing a robust,

multidimensional evaluation of VTE and bleeding risk. Furthermore, by simultaneously evaluating both efficacy (VTE prevention) and safety (clinically relevant bleeding risk) outcomes across multiple chapters, this thesis provides a balanced and clinically meaningful assessment of the benefit-risk profile associated with the use of biomarkers and genetic risk factors to guide thromboprophylaxis in ambulatory cancer patients.

7.5 Conclusions

This doctoral thesis provided a multidimensional evaluation of VTE and bleeding risk in ambulatory cancer patients by integrating genetic factors, circulating biomarkers and advanced predictive modeling. It established that inherited thrombophilia, such as non-O blood types, FVL and Prothrombin Factor II G20210A, are significant predictors of VTE, and that select biomarkers such as, d-dimer, neutrophil-lymphocyte ratio and complete blood count components, can offer additional predictive value depending on timing of measurement. Additionally, associations between inflammatory and cardiac biomarkers (i.e., GDF-15, NT-proBNP, hs-TnT, and CRP) and VTE and bleeding risk were observed. This suggests an interplay between inflammation, cardiac dysfunction and coagulation in this population – a potentially important perspective to capture in risk assessment models. Furthermore, this thesis demonstrated that integrating genetic factors and circulating biomarkers alongside clinical risk factors in machine learning algorithms can enhance risk stratification. By leveraging both traditional and novel biomarkers, it may help to capture the multifactorial nature of cancer-associated thrombosis and bleeding. Collectively, these findings underscore the significance of using a more personalized, multifactorial and biomarker-informed approach to thrombotic and bleeding risk prediction in cancer patients.

7.6 References

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