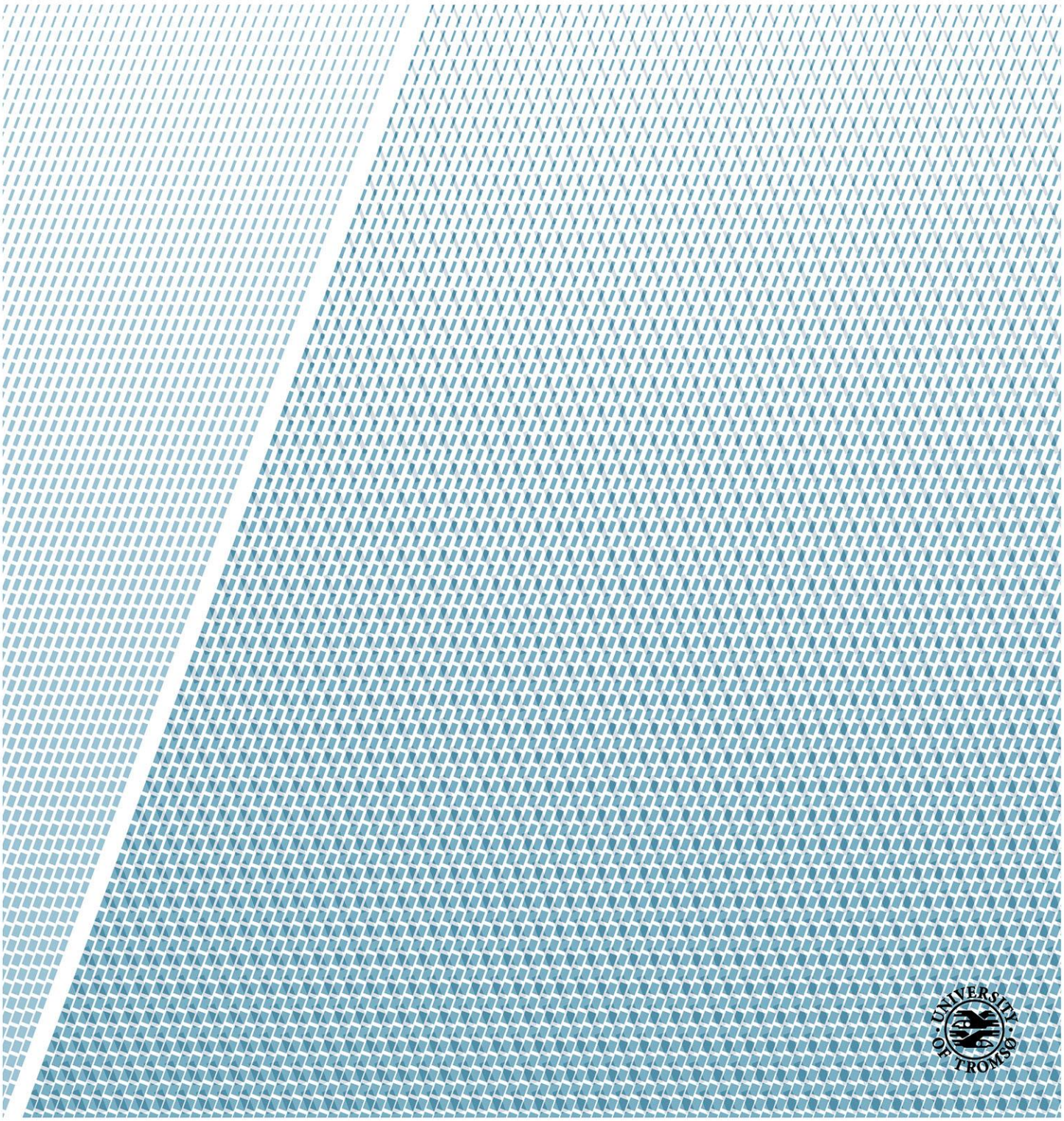
Benedikte Paulsen

Risk assessment models for prediction of venous thromboembolism in ambulatory cancer patients – A literature review

Master thesis, MED-3950/MK-14

Tromsø: Medisine, program of professional study
Faculty of Health Sciences
UiT – The arctic University of Norway, 2019



Preface

Thrombophylaxis is the cornerstone in the prevention and treatment of venous thromboembolism (VTE). However, use of anticoagulants comes at a cost of substantial increased risk of bleeding. In cancer patients, both the risk of VTE and bleeding complications are especially elevated, and although tremendous amount of research on cancer and cancer-related VTE exist, the tools for safely identifying patients at high risk of VTE are still lacking. Hence, resulting in not recommending routinely primary thrombophylaxis to ambulatory cancer in current guidelines.

The purpose of the current thesis was to create a general summary of knowledge on risk prediction models in ambulatory cancer patients.

Firstly, I would like to thank Eirik Reierth at the Science and Health Library at UiT – The artic University of Norway for the well-appreciated navigation in the jungle of scientific literature and databases, and specifically, the help with identifying terms and building of a systematic search.

The project was carried out supervised by Professor John-Bjarne Hansen and Professor Sigrid K. Brækkan at K.G. Jebsen Thrombosis and Expertise Center (TREC), Department of Clinical Medicine at the UiT – The Artic University of Norway. I would like to thank you both for always being available for guidance in my times of frustration, your genuine interest and competence in the field of Venous Thromboembolism never ceases to amaze me.

Tromsø, June 2019

Benedikte Paulsen

Table of contents

Summary

Background: Venous thromboembolism (VTE) represents a significant burden of health for those affected, and complications after a VTE are especially pronounced in cancer patients. One fifth of all cancer patients will develop a VTE during their disease. Routine primary thrombophylaxis is not recommend in ambulatory cancer patients due to lack of tools to identify those at especially high risk, as anticoagulants comes with a substantial risk of major bleeding.

Aim: The aim was to perform a systematic literature search to gather existing information, summarize and evaluate the evidence on prediction models for VTE in ambulatory cancer patients.

Methods: Published scientific articles were obtained by systematically searching the Medline and Embase databases, and in addition, a free-text search in PubMed was applied to ensure optimal coverage of the search.

Results: A total of 22 articles on risk assessment models (RAMs) in ambulatory cancer patients was identified, of these 9 papers presented novel models and the rest validated one or more RAM. The identified scores were the Khorana risk score (2008), Vienna CATS score (2010), Protect score (2012), CONKO score (2013), ThroLy score (2016), ONKOTEV score (2017), COMPASS-CAT score (2017), Tic-onco index (2018) and Vienna nomogram (2018). The Khorana risk score has been validated the vast majority of the identified studies, with main critique is that >50% of patients fall into an intermediate risk category. Further, The Vienna CATS, Protecht, CONKO, COMPASS-CAT and Vienna nomogram has been externally validated and showed somewhat varying results.

Conclusion: Several RAMs on cancer-related thromboembolism in ambulatory cancer patients are developed. Although promising performance is found for many of the scores, most validation studies are of suboptimal quality, and the clinical feasibility of the models are yet to be established. Additionally, continuously effort is needed to address the bleeding risk in this patient group.

Abbreviations

AUC – Area under the curve

CAT – Cancer-associated thrombosis

CATS – Vienna cancer and thrombosis study

CI – Confidence interval

DVT – Deep vein thrombosis

GRADE - The Grading of recommendations Assessment, Development and Evaluation

HR – Hazard ratio

IR – Incidence rate

KRS – Khorana risk score

LMWH – Low molecular-weight heparin

NPV – Negative predictive value

PE – Pulmonary embolism

PPV – Positive predictive value

ROC – Receiver operating characteristic

RR – Relative risk

VTE – Venous thromboembolism

1. Introduction

Cancer is the common term for diseases caused by uncontrolled cell growth and division, with potential to invade and spread to remote parts of the body. Apart from shared patterns of basic mechanisms, the cancer term grasps over a hundred different diagnoses, often categorized from source organ of malignancy or histological features, and includes a whole spectre of severity, survival and mortality. The classical triad of treatment include surgery, chemotherapy and radiation, but as cancer is a hot topic of research, several novel treatment strategies are emerging at a high pace.

Venous thromboembolism (VTE), a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease after myocardial infarction and stroke. A DVT is the formation of a blood clot in the valve pockets in the deep veins, which can interrupt the venous return and lead to obstruction of blood flow. A dislodging of thrombi leads to an embolus, able to follow the bloodstream to the pulmonary arteries where it results in a blockage located where the size of the emboli succeeds the lumen diameter. The symptoms following a classical DVT are unilateral swelling, pain, redness and heat of the affected extremity, and following a PE are pleuritic chest pain, couching, tachypnea and eventually death by collapse.

1.2 Cancer

1.2.1 Epidemiology

Cancer is the leading cause of morbidity and mortality, with an estimated incidence of 14.1 million new cases annually worldwide in 2012 (1). The incidence of cancer is increasing and the International Agency of Research on Cancer estimated 18.1 million incident cancers diagnoses and 9.6 million deaths due to cancer in 2018 (2). In a global perspective, researchers report that approximately 170 million years of healthy life are lost due to malignant disease (3). The number of incident cancer diagnoses in Norway was approximately 33 000 in 2016, and the pooled incidence rates for all cancer types increased with 0.9 % in men and 5.5% in women in the period 2013-2017 compared to the previous period from 2008-2012 (4).

1.2.2 Pathophysiology

Grasping the pathology behind a disease capable to defeat the very fundamental processes of human life seems impossible. In a review from 2000, Douglas Hanahan and Robert Weinberg

first presented the 'Hallmarks of cancer', which represented a paradigm shift in the understanding of cancer biology, and gave a common ground to later discuss the field. The Hallmarks comprise of central traits present for a neoplasm to arise and grow. The six initial hallmarks are: 1) enhance self-proliferative pathways, 2) avoid growth suppressors 3) avoid apoptosis 4), promote angiogenesis 5) facilitate infinite replication and 6) activating invasion and metastasis (5). As of an update in 2011, four new hallmarks were added to the list, evade immune destruction, modification of metabolism, genetic alterations (i.e. instability and mutations), increased tumour-promoting inflammation (6).

1.2 Venous Thromboembolism

1.2.1 Epidemiology

The estimated annual incidence of VTE is 1-2 per 1000 person-years, and the incidence increase by increasing age (7). Complications following a VTE include recurrent VTE, post-thrombotic syndrome in the affected extremity, pulmonary hypertension and bleeding complications from subsequent anticoagulant therapy. VTE is a major cause of mortality and morbidity, with a one-month case-fatality rate of 5-10% after a DVT and 8-16% after a PE (8). Moreover, VTE is a prominent cause of disability-adjusted life years (DALYs) lost worldwide (9). A VTE-event is categorized into provoked if known risk factors can be identified at diagnosis, and if not, the event is categorized as unprovoked. Risk factors comprise of inherited (prothrombotic genotypes) and acquired (age, cancer, trauma surgery, immobilization, pregnancy) factors (10).

1.2.2 Pathophysiology

The cornerstone of understanding the pathophysiology of VTE was presented by Rudolph Virchow in 1856. Virchow`s triad consisted of three contributing mechanisms including turbulent blood flow (stasis), alterations in blood composition (hypercoagulability) and vessel wall injury (endothelial impairment). The site of predilection of clot formation is in the venous valves of the large vessels which are subject to localized hypoxia due impairments in blood flow (11). This tends to results in an activation of the endothelium which recruit procoagulant responses, hence, initiate thrombus formation.

1.3 Cancer and venous thromboembolism

1.3.1 Epidemiology

Cancer is established as one of the leading risk factors for VTE (12, 13). According to epidemiological estimations, cancer patients are subject to 20 % of all incident VTEs occurring in the general population (14, 15). Patients with malignant disease have an overall four to seven-fold increased risk of experiencing a VTE compared to the general population (16, 17). The cumulative incidence of a cancer-related VTE is estimated to range from 1% up to 12% (18-20). The observed divergence may origin from differences in source populations studied, length of study period and validation of VTE events and cancer diagnoses. Experiencing a VTE during the course of the malignant disease is associated with poor prognosis (21). Further, it has been found that about 74% of incident cancer-related VTEs occur in an ambulatory setting (22).

1.3.2 Pathophysiology

The haemostatic system is an intricate system responsible for maintaining a steady state for the vessels and is highly linked to inflammation. The haemostatic system and cancer progression has been tightly linked. Several factors of malignant disease contribute to a pro-thrombotic state in cancer (e.g. site and stage of the cancer (18) and anticancer regime (19)). Oncogenic cells have been found to promote activation of the haemostatic system through platelet activation and aggregation (23) and increased expression of tissue factor (24-26). Moreover, cancer patients have been found to have elevated laboratory values of essential components of the coagulation system (i.e. thrombin-antithrombin complex, D-dimer, prothrombin fragment 1+2, protein C-resistance (27)). The elevated parameters are thought to origin from enhancement of cancer growth and metastatic potential (28).

1.3.3 Primary thrombophylaxis in ambulatory cancer patients

The Cochrane Collaboration performed a systematic review to synthesize current knowledge and evaluate the efficacy of primary thrombophylaxis in ambulatory cancer patients receiving chemotherapy. They found that low-molecular heparin (LMWH) reduced the incidence of symptomatic VTE-events (RR 0.62, 95% CI 0.34-0.88) compared to a control group without intervention (29). However, a trend towards LMWH increasing the risk of major bleeding (RR 1.57, 95% CI 0.69-3.6) was also found compared to the control group. In the updated review published in 2016, the authors conclude that further evidence in identifying the risk-to-benefit ratio of thrombophylaxis is needed. Especially knowledge on identifying

those with highest risk of a cancer-associated thrombosis (CAT) is needed before routinely giving ambulatory cancer patients with chemotherapy anticoagulation (30).

1.4 Predictors and risk prediction models

1.4.1 Aetiology and prognostic research

In epidemiology, there is a distinct difference between etiological and prognostic research (31). First, aetiological research intent to evaluate the causal interplay between a component and the effect on an outcome of interest, based on a possible observed effect. Then, a research question is raised, data is gathered and analysis is carried out while adjusting for potential confounding factors that may interfere. In contrast, prognostic research aim to predict future events (positive or negative) using risk factors (e.g. predictors) to investigate whether they modify the probability of an outcome. Predictors are not necessarily causal to the outcome, but can serve as a proxy for an underlying process that is not measurable.

1.4.2 Development of risk assessment models

The making of a prediction model is a time-spanning process that comprise of several steps. Prospective cohort studies is regarded as the most optimal study design to conduct prognostic research (32). Randomized controlled trials (RCT) can also be used, but may have limited generalisability due to a homogenous population. According to a method article by Moons and colleagues, prognostic research should focus on absolute risk as opposed to relative risks (32). This makes case-controls an unsuitable study design in prognostic due to the difficulties in calculating absolute risks. There is no consensus on the best method of selecting candidate predictors to incorporate in a prediction model. However, a multivariable approach is most often used (33).

Predictors can be previously known from literature or identified in the population of interest, and then, often based on the strength of association (β-coefficients), a weighted equation or nomogram is established. Cut-off values will often be set for the model in order to stratify individuals into risk groups. The finished model is tested through internal validation (i.e. testing of the model in the same population). Several methods for internal validation exist, but splitting of the original population where the model is developed in one part and validated in the other is one of the most common (34).

1.4.3 External validation and performance of risk assessment models

For a proposed RAM, external validation is necessary to test for the goodness-of-fit of the model in independent, yet relevant, population. The ability of calibration and discrimination of the model is tested to evaluate the overall performance. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) collectively represent statistical calculations of the performance of a two-by-two classification test (35). The sensitivity is the proportion of real positives classified as such in the total amount categorized as positives by the test. Vice-versa, the specificity is the proportion of real negatives classified as such in the total amount classified as negatives by the test. In current thesis, the sensitivity represent the probability of being in the high risk group given a VTE. The specificity represent the probability of being in the low risk group given VTE-free. Unlike sensitivity and specificity, the PPV and NPV are statistical features of a two-by-two matrix that are dependent on the prevalence of the outcome of interest. The PPV is the proportion of true positives of the total amount of positive outcomes by the test. Correspondingly, the NPV is the proportion of true negatives of the total amount of negative outcomes by the test. In current thesis, the PPV represent the probability of a VTE if categorized to the high risk group. The NPV represent the probability of not experiencing a VTE if categorized in the low risk group.

The sensitivity and the 1-specificity can be used to plot a receiver operating curve (ROC) with an accompanying area under the curve (AUC), often referred to as concordance statistic (c-statistic). The c-statistic range from 0 to 1.0, and a value of 0.5 indicate the test to be no better at predicting an outcome than random chance. A c-statistic of 1.0 indicate that a model predict all subjects to the true outcome. If the performance of the model yield good discriminative ability of identify high- and low risk patients, the model is prompt to be tested in a controlled clinical setting to authenticate the real performance.

In the process of developing and implementing a prognostic model, there are a few fundamental elements that can be identified; 1) available efficient intervention, 2) effective screening test (risk assessment model (RAM)), 3) morbidity/mortality and/or financial benefits of early intervention/prevention (35). In terms of cancer related thrombosis, thrombophylaxis is proven efficient in preventing VTE-events. Hence, identifying subjects at high risk is crucial.

1.4 Aim of the thesis

The aim of this thesis was to perform a systematic literature search to gather existing information, summarize and evaluate the evidence on risk assesment models for VTE in ambulatory cancer patients.

2. Methods

2.1 Literature search

2.1.1 Databases

Medline and Embase are the two databases that were used to identify relevant articles using the Ovid search platform. Additionally, a free-text search in PubMed was performed in order to identify published papers not yet indexed in the databases. Medline (Medical Literature Analysis and Retrieval System Online, or MEDLARS Online) is a database produced by the U.S National Library of Medicine, and includes bibliographic information from academic journals covering medicine, nursing, odontology, veterinary medicine, health care and preclinical sciences. Embase (Excerpta Medica database), produced by Elsevier, contains over 32 million articles from over 8500 medical journals from different countries (West European dominance) with a specific focus on pharmacology, public health and substance abuse. The two different databases were chosen due to slightly different fields of interest and amount of papers. However, there is a major overlap of articles.

2.1.2 Search strategy and data collection

The Ovid search platform was used to access the two databases (Medline and Embase). The search was modified slightly in the different databases due to different indexations. Medline utilizes the MeSH terms for indexations, and Embase uses the Emtree terms. In the process of identifying relevant indexations, central known articles were examined, relevant terms were extracted and formed the basis for the advanced search. The search was performed 1th of February 2019. The finalized searches applied are displayed in the appendix. Supplementary table 1 displays the search in Medline, supplementary table 2 displays the search in Embase and supplementary table 3 displays the free-text search in PubMed.

A modified PRISMA chart for the approach and selection of relevant papers was utilized. The PRISMA statement comprise of a checklist and flow diagram. It is an evidence-based tool to aid in transparent reporting and evaluation in systematic reviews on previously

published research (36). A modified PRISMA flow diagram is displayed in figure 2, showing origin of papers, screening, exclusions and number of included papers.

2.1.3 Inclusion and exclusion criteria

Cancer and VTE are both topics that have been thoroughly researched throughout modern medicine history. Thus the amount of articles published is substantial. In order to narrow the search, limitations had to be applied in the search strategy. The first risk assessment model (RAM) was introduced in 2008 by Khorana and colleagues, and the search included papers published from 2008 and onwards. Further, the crude search was limited to English language and studies indexed as human. Review articles and in vitro studies was excluded, as well as studies in special populations (i.e. paediatric).

2.1.4 Data extraction

All identified articles from the three databases were exported to an Endnote library. Further, duplicates were identified and removed. Articles included from the full-text screen was sorted on based on whether a novel RAM was introduced or studies regarded only validation. The articles was sorted in tables of the current RAM that were investigated. Hence, articles will be presented in several the tables if it reports findings on multiple RAMs.

2.2 GRADE

The Grading of recommendations Assessment, Development and Evaluation (GRADE) approach is constructed as a tool to critically evaluate evidence and form the basis for recommendations and guidelines used in health care (37, 38).

3. Results

There were 534 articles in the crude search (Figure 2). After removing duplicates (n=66), a total of 468 underwent a title screen, resulting in 206 for abstract screening. This process excluded 133 papers, leaving 53 ready for a full-text screen. After the full-text screening process using predetermined inclusion- and exclusion criteria, the total number of eligible papers fitting the research question was 21. The articles are arranged in tables according to the risk assessment model (RAM) investigated. Some of the identified articles explored several RAMs, and will therefore be presented in several tables with the findings of the respective RAMs.

3.1 Identified risk assessment models

3.1.1 The Khorana risk score

The Khorana risk score (KRS) is the first and most researched (RAM), and was developed by Khorana and colleagues in 2008 aiming to stratify ambulatory cancer patients receiving chemotherapy into low-, intermediate and high- risk of VTE in the six months following (39). Summary of identified papers on the KRS are presented in table 1. The prediction model was developed through a multivariable logistic regression, whereas a weighted risk score based on the strongest estimates were established. The study population was selected from the Awareness of Neutropenia in chemotherapy (ANC) study group registry, a multicentre prospective observational cohort of cancer patients about to initiate chemotherapy. A split sample approach was used, where the RAM was developed in one part (n=2701) and internally validated in the other (n=1365). The final model consisted of the following parameters: 1) Site of cancer (very high risk; pancreas, gastric and high risk lung, lymphoma, gynaecologic, bladder, testicular), 2) prechemotherapy platelet count, 3) anaemia (haemoglobin level≤10g/L) or use of erythropoietic agents, 4) prechemotherapy leucocyte count, and 5) BMI > 35 kg/m^2 (Table 10). Very high risk cancers amounted as 2 points, the remaining parameters contributed 1 point each to the total score. The model stratified patients into three groups; low- (score 0), intermediate- (score 1-2) and high risk (score of ≥3) of VTE. The performance of the KRS displayed a 0.3% rate of VTE in low-risk, 2.0% in intermediate-risk and 6.7% in high-risk category in the validation cohort, which represented a C-statistic of 0.7 at six months.

Mandala and colleagues published in 2012 findings from exploring the KRS in a multinational, retrospective phase I trial of 1415 ambulatory patients where the vast majority had advanced cancer (40). Phase I trials are also called (“first in human”) studies, the population thereby comprised of cancer patients receiving novel anticancer therapy, introducing a toxicity factor to the population. The cumulative incidence of VTE was 1.5% in the low risk group, 4.8% in the intermediate risk group and 12.9% in the high group. They found that the median time-to-VTE was significantly shorter in those in the high-risk group of the KRS than those in the intermediate-risk group (23 days vs 44 days). The ROC curves showed an overall c-statistic of 0.65 at three months, and this is somewhat lower than the 0.7 found by Khorana at al. at six months. Likewise, Kim and colleagues, concluded that the score was able to predict VTE 6 months after initiation of anticancer treatment in a retrospective study of 90 ambulatory cancer patients with metastatic disease (41). The rate of VTE was 24% in low

risk patients, 20% in the intermediate risk group and 37% in the high risk group. However, the study included both VTE and myocardial infarction (MI) as outcomes, and no objective validation of events was performed.

In 2015, two studies exploring the KRS were published. Panizo and colleagues first explored the KRS in 1108 outpatients receiving chemotherapy in Canada, and found that 45.8% (n=505), 47.4% (n=523) and 6.8% (n=75) of patients were allocated in the low-, intermediate- and high risk group, respectively (42). The proportion of VTE events was 3.4% in the low risk group, 6.3% in the intermediate group and 10.7% in the high risk group. In a study by Lustig et al., they incorporated the KRS into a computerized program to automatically categorize patients into low (score 0-1) and intermediate/high (score ≥2) risk groups. They found a rate of VTE of 4% in the low risk group and 11% in the intermediate/high risk group (43). Of note, neither of these two studies further evaluated performance of the score as that was not the primary aim.

Some of the identified articles aimed to validate the KRS in subtypes of cancer (i.e. pancreatic, gastric and lung cancer). First, in a population of 178 patients with pancreatic cancer starting chemotherapy, van Es and colleagues found the cumulative incidence of VTE in the intermediate - (8.2% at six months and 14.0% at 12 months) and high risk groups (9.5% at six months and 10.1% at 12 months) to be essentially similar. Concluding that the KRS was not able to discriminate between intermediate- and high risk patients for developing VTE among pancreatic cancer patients (44). Further, findings from a retrospective study cohort of 172 pancreatic cancer patients receiving chemotherapy was published by Kruger et al (45). The rate of VTE was 12% for those in the intermediate risk group and 19% in the high risk group. However, only 65% of the population was available analysis of the KRS due to missing data or excluded due to treatment with anticoagulants at baseline.

In a retrospective study of 112 gastric cancer patients, 59 (52.7%) patients were classified as high risk by the KRS of which 9 (15%) incident VTEs occurred during a median follow up of 21.3 months (46). The study reported a sensitivity of 69%, specificity of 49.5% PPV of 15.3% and NPV of 88.4% of the KRS in the study. The majority of subjects experiencing a VTE was classified in the intermediate risk group, represented by the low PPV.

Lung cancer is considered as a “high risk” cancer by the Khorana risk score, and three of the studies have performed an external validation in this patient group. First, a retrospective study of 719 patients found the cumulative incidence in patients categorized to the intermediate risk group (5.2% at 3 months and 6.2% at 6 months) and high risk group (5.1% at 3 months and 6.3% at 6 months) essentially the same (47). Of note, the study had a 78% mortality at a median follow up of 15.2 months. In another retrospective study of 117 lung cancer patients, the rate of VTE was 15% in the high risk group and 17.5% in the intermediate risk group (48). The test statistics displayed a sensitivity of 10%, specificity of 100%, PPV of 17% and NPV of 83% with a c-statistic of 0.81. However, only two events occurred in the high risk group. A prospective, global cohort consisting of 1980 lung cancer patients investigated the KRS. The rate of VTE was found to be essentially the same for patients in the low (6.4%), intermediate (6.5%) and high risk (5.4%) group six months after treatment initiation. Of note, the study included different ethnicities and many patients were treated with novel anticancer treatment (49).

Patell and colleagues investigated the KRS in a retrospective cohort of hospitalized cancer patients (50). The proportion of VTE increased from 2.5% in the low risk group to 5.5% in the high risk group. They reported the odds of VTE was 2.5-fold higher (OR 2.5, 95% CI 1.3-4.9) in those with a KRS ≥2 than in those with a KRS of 0 or 1. The study excluded 21.1% of the study population in the analysis. The article concludes that a threshold of 2 points at the KRS may result in a better stratification than the conventional 3 point threshold.

In 2017, van Es and colleagues published findings from a multinational prospective cohort study comprising of 876 patients with advanced solid cancers (51). The overall 6-month competing risk cumulative incidence was 6.5% (95% CI 4.9-8.3%). At 6 months, the cumulative incidence in the high risk group was 6.0%. And at a cut-off of ≥3 points of the KRS, the c-statistic was 0.50 (95% CI 0.42-0.57) in 260 patients about to initiate chemotherapy. The c-statistics remained essentially unchanged when calculated in the full cohort. High- compared to low- risk score was not associated with VTE in competing risk by death analysis (sub distribution hazard ratio: 1.0, 95% 0.46-2.2).

A recently published meta-analysis consisting of 34 555 unique ambulatory patients collected from 45 articles and 8 abstracts evaluated the KRS (52). The distribution was 19% in the low risk group, 64% in the intermediate risk group and 17% in the high risk group. The

corresponding cumulative incidence of VTE was 5.1% (95% CI 3.9-6.5%), 6.6% (95% CI 5.6-7.7) and 11.0% (95% CI 8.8-13.8) at six months in the low-, intermediate- and high risk groups, respectively. Interestingly, they found that of all patients experiencing a VTE within the first 6 months, only 23.4% had been allocated the high risk group (≥3 points) by the KRS. Meaning that the majority of VTE-events occurred outside the high risk group.

3.1.2 The Vienna CATS score

In 2010, the first modification of the KRS was published. Ay and colleagues found that adding D-dimer and soluble P-selectin inproved the prediction of VTE-events in their cancer patient population. Identified articles regarding this RAM is displayed in table 2. The risk score was developed in a prospective cohort of cancer patients (newly diagnosed or advancement after complete or partial remission) (53). In total, 7.4% (n=61) experienced a VTE during a median follow-up of 656 days. The expanded model incorporated D-dimer ≥1.44 µg/ml and P-selectin ≥53.1ng/ml at baseline, which added 1 point each to the KRS and stratified patients to 6 groups with a score from 0 to 5 (table 11). The cumulative probability of getting a VTE at 6 months was 35%, 20.3%, 10.3%, 3.5%, 4.4% and 1.0% for the 5 groups in descending order (high to low risk group). In comparison, the KRS alone displayed a cumulative probability of VTE of 17.7% (95% CI 11.0-27.8%) at a score of ≥3 or higher, 9.2% (95% CI 6.2-14.7%) in the group of 2 points, 3.8% (95% CI 1.9-7.4%) in those with 1 point and 1.5% (95% CI 0.6-3.9%) in the group with 0 points. At a cut-off of 5 points or higher by the Vienna CATS score, the test showed a sensitivity of 19.1% and specificity of 98.2%, and a positive- and negative predictive value (PPV and NPV) of 42.9% and 94%, respectively, at 6 months. In comparison, applying a threshold of ≥3 in the Khorana risk score, the sensitivity and specificity was 31.4% and 91.9%, respectively, with a PPV of 21.1% and a NPV of 94.9%.

In an external validation by van Es and colleagues, the Vienna CATS score at a threshold of ≥5 yield a C-statistic of 0.57 (95% CI 0.48-0.66) at 6 months, which was higher that the c-statistic found for the KRS in the population (51).

3.1.3 The PROTECHT score

In 2012, Verso and colleagues presented another modification of the KRS called the Protecht score after the randomized controlled study (RCT) in which it originated (54). A summary of identified articles on the RAM are presented in table 3. The model was expanded by adding platinum or gemcitabine-based chemotherapy regimens to the existing parameters in KRS (table 12). The placebo arm of the RCT was explored to develop a score dichotomizing cancer patients into high (≥3 points) - and low (0-2 points) risk. Stratification resulted in 32.2% of the patients allocated to the high-risk group and 67.2% to the low risk group, and of the total 15 VTE-events, 66.7% occurred in the high risk group. The authors also applied the KRS to the study sample in order to compare it with the Protecht score, and used three points or higher as a threshold between high and low risk groups. The Protecht score identified 67% of VTE-patients as high risk and the KRS identified 33 % as high risk.

The score was validated in a retrospective cohort of lung cancer patients. The proportion of patients that developed a VTE was essentially similar for patients allocated to the low (16%) - and high (17.7%) risk group by the Protecht score. Accordingly, the RAM was found to have a sensitivity of 10%, specificity of 78%, PPV of 18% and NPV of 84% when the cut off was set to 3 points or higher (48).

Validating of the risk score was done by van Es and colleagues. The C-statistic was found to be 0.54 (95%CI 0.45-0.66) at a threshold of 3 points, in patients receiving chemotherapy (51).

3.1.4 The CONCO score

A risk score by Pelzer and colleagues was identified in the search, however, initially excluded since full text not was obtainable in English, only German (55). Articles on the risk score are displayed in table 4. The model was included again since validation studies in English was identified. According to an external validation, the score is a modification of the KRS called the CONKO score. BMI has been excluded as a predicting variable and replaced by WHO performance status ≥2 (table 13). The score was externally validated by van Es and colleagues, where they found the cumulative incidence of VTE to be 5.2% at 6 months at a threshold of ≥3 point (51). The corresponding c-statistic was found to be 0.5 (95% CI, 0.44-0.57). The

CONKO risk score was found inferior to the other evaluated RAMs (KRS, Vienna CATS score and Protecht score) in terms of discriminatory ability between high and low risk.

Rupa-Matysek and colleagues validated the risk score in a retrospective cohort of 118 lung cancer patients (48). The proportion of VTE was 15% in the high risk group (≥3 points) and 17% in the low risk group (<2 point). The sensitivity was 55%, specificity of 48%, PPV of 15% and NPV of 82%.

3.1.5 ThroLy score

A RAM developed to predict thrombotic events (venous and arterial) in patients with lymphoma, published by Antic and colleagues was identified (56). The study population included 1820 patients with confirmed diagnosis of non-Hodgkin lymphoma, Hodgkin lymphoma and chronic lymphoid leukaemia/small lymphocytic lymphoma, treated at a cancer centre in Serbia (table 5). Through a split sample method, a RAM was developed in one part of the study and validated in the other. Parameters associated with the outcome in univariate analysis was included in a multivariate model, and from this, regression coefficients where weighted to form the RAM. The final RAM is displayed in table 14. The RAM had a maximum score of 10 points, dividing participants to low risk (score 0-1), intermediate (score 2-3) and high risk (score ≥4). When applying a threshold of ≥4 to the validation cohort, the test showed a sensitivity of 64.7%, specificity of 90.2%, PPV of 28.9% and a NPV 97.6%. Corresponding c-statistic was 0.86. Independent studies validating the RAM was not identified.

3.1.6 The ONKOTEV score

From a cohort of cancer patients with solid tumours enrolled in Naples (Italy) and Leipzig (Germany), a risk stratification model called ONKOTEV was developed in 2017 (table 6) (57). Researchers followed 842 cancer patients for a median of 8.3 months where 8.6 % of patients experienced an incident VTE. In addition to symptomatic VTE, the study also included asymptomatic VTE. All participants were screened for DVT at baseline and at six months follow up, and PE was identified though investigating the most recent cancer-associated CT scan. The risk score comprised of the parameters that were independently significant associated with VTE, where each of the following amounted as one point; a Khorana risk score of >2, previous

VTE, metastatic disease and vascular/lymphatic macroscopic compression (table 15). The authors included analysis on the KRS for comparison. Stratification on the ONKOTEV score of 0, 1, 2 and >2 displayed a cumulative probability of VTE at 12 months of 3.7% (95% CI 1.1-6.3%), 9.7% (95% CI 6.5-12.94%), 19.4% (95% CI 10.1-28.7) and 33.9% (95% CI 20.3-47.4%). For the KRS, the cumulative incidence was 8.8% in the low risk group (0 points), 9.2% in the intermediate risk group (1-2 points) and 21.7% in the high risk group (>2 points) at 12 months. The C-statistic for the ONKOTEV score was better than for the KRS at 6 months (0.75 vs 0.58). No studies further validating this score was identified through the search.

3.1.7 The COMPASS-CAT score

In addition to the ONKOTEV score, a paper presenting a RAM derived from the "the prospective comparison of methods for thromboembolic risk assessment with clinical perceptions and awareness in real life cancer patients-cancer associated thrombosis" (COMPASS-CAT) study was published in 2017 (58). The score included parameters from a multivariable analysis that were significantly associated with VTE in the population of ambulatory breast, colorectal, lung and ovarian cancer patients receiving chemotherapy (Table 16). The aim was to make a risk assessment model utilizable also after chemotherapy has been initiated. Predictors in the model were somewhat more comprehensive than previously referred scores, and included comorbidities (cardiovascular disease), recent hospitalization (<3 months), cancer-related factors (stage, time since diagnosis, treatment and presence of a central venous catheter), platelet count (≥350 x 10^9/L) and previous history of VTE, all weighted by the strength of association to the outcome. The maximum score was 28, and the threshold between low/intermediate- and high risk was set to a score of 7 or higher. The rate of VTE was 1.7% (n=9) in the low/intermediate risk group and 13.3% (n=68) in the high risk group. The test performance was calculated to a have a NPV of 98% and a PPV of 13%, and a sensitivity of 88% and a specificity and 52%. The c-statistics at six months was 0.85.

In the study by Rupa-Matysek and colleagues, the COMPASS-CAT was evaluated in a population of lung cancer patients undergoing ambulatory chemotherapy (48). The study found the proportion of VTE events to be 23.8% in those categorized to the high risk score according to COMPASS-CAT. With a threshold of 7 points or more, the c-statistic was found to be 0.89, and a sensitivity of 100%, specificity of 35%, PPV of 24% and NPV of 100%. The

COMPASS-CAT was found better at discriminating high-and low risk patients than the KRS, CONKO and Protecht in the population.

3.1.8 The TiC-Onco

Prothrombotic genotypes have been thoroughly explored in the field of VTE research in the recent years. The interest of genetics in cancer-related VTE have also increased as they are fix as opposed to other factors following a cancer disease. In 2018, a risk model that incorporated genetic risk factors to differentiate risk cancer patient on risk of thromboembolism was presented (59). A observational cohort comprising of 391 patients eligible for outpatient chemotherapy with a recent diagnosis of upper- or lower GI, lung or pancreatic cancer were followed for 6 months, whereas 18.2% (n=71) experienced a VTE. Martin and colleagues used the Thrombo inCode® (TiC) model, a model originally developed to diagnose inherited thrombophilia, and modified it to current risk model, the Tic-Onco model. The TiC-onco index is a commercial product and therefore not available in most laboratories. The p-values of the different parameters in the RAM are displayed in table x.

In those allocated the high risk group of TiC-onco, 37% experienced a VTE during a follow up of 6 months. The proportion of VTE in the low risk group was 5.6%. The cut-off was set to match the specificity of the KRS in the population (80%). The C-statistic was found to 0.73 with a 49% sensitivity, 81% specificity, 37% PPV and 88% NPV. In comparison, the KRS displayed a C-statistic of 0.58 with lower sensitivity (22%) and PPV (22%) in the study. Like other studies, the authors found the majority of VTE-events to occur in the intermediate risk group according to the KRS. There were no studies validating this score identified.

3.1.9 The CATS nomogram

In 2018, researchers from Vienna who originally presented the Vienna CATS score published a new risk prediction model called the CATS nomogram (60). It was developed and validated in two independent cohorts. Data from the Vienna Cancer and Thrombosis study was used as a development cohort (same population as Vienna CATS score), and data from the Multinational Cohort Study to Identify Cancer Patients at high risk for Venous Thromboembolism (MICA) was used for the external validation. The source population was ambulatory cancer patients was that were followed for 6 months (further details displayed in Table 9). Authors aimed to make a more simplified RAM for VTE in ambulatory cancer patients,

to increase the clinical applicability of the model. A total of 11 prognostic parameters were identified through univariate analysis. Cancer site in three levels (high, intermediate and low) and D-dimer as a continuous scale yield the strongest estimates and where selected to the nomogram (Figure 1). The model was able to predict the six-month cumulative incidence (5.7%) equal to the observed in the cohort (5.7%, 95% CI 4.5-6.9). A c-statistic of 0.66 (95% CI 0.63-0.67) was calculated in the development cohort. In the external validation, the nomogram predicted the mean 6-month cumulative incidence to be 6.4%.This was in line with the observed six-month cumulative incidence (6.3%, 95% CI 4.7-8.2), and with a C-statistic of 0.68 (95% CI 0.62-0.74). At a 10% predicted cumulative incidence cut-off, the model showed a sensitivity of 21%, specificity of 87%, PPV of 9% and NPV of 95%. Through decision curve analysis, the authors suggested considering thrombophylaxis to patients with a predicted six-month risk between 6 and 11%.

No studies furthering validating the CATS nomogram was identified.

4. Discussion

The current literature search identified a total of 9 novel risk assessment models (RAM) developed to predict incident VTE-events in cancer patients. In addition, 12 studies aimed to validate one or more score in other cancer populations.

The first and most validated risk assessment model (RAM) for ambulatory cancer patients is the Khorana risk score (KRS) (39). Included parameters are easily-accessible in clinical practice, and the score stratifies patients in low, intermediate and high risk groups. Initially a C-statistic of 0.7 was found, but in later validations this was found decreased to 0.65 (40) and 0.5 (51). A c-statistic of 0.5 indicate that the model is no better at predicting than a coin toss. Further, the KRS displayed poor discriminating ability for VTE in pancreatic- (44), lung- (47-49) and gastric cancer (46). These cancer types are typically associated with high risk of VTE (17, 18, 61). The biggest limitation to the KRS is that the majority of VTE-events occurs in patients allocated to the intermediate risk group, represented by findings of low positive predictive value. To further support this conclusion, a meta-analysis found 76% of incident cancer-associated VTEs occurred in the intermediate and low group at the conventional threshold of ≥3 points (52).

As an attempt to improve prediction of cancer-associated VTE, several modifications of the KRS has been introduced. First, Ay and colleagues added a threshold of measured D-dimer and P-selectin (53). Second, Verso and colleagues added treatment with specific chemotherapeutic regimes (platinum-based or gemcitabine) (54). Both modifications yielded better prediction in internal validation when compared to KRS in the study populations. And third, Pelzer and colleagues removed the BMI parameter and added performance status to their model, the CONKO score (55). In a prospective cohort of cancer patients with solid tumours (unrelated to any of the source populations), researchers found the KRS, Vienna CATS, CONKO and Protecht score to perform poorly in terms of predicting CAT within 6 months after initiating chemotherapy (51). However, the Vienna CATS and the Protecht score were found to better at discriminating between high- and low risk than the KRS and CONKO score.

Prediction models more complex in nature has been presented in the recent two years. The COMPASS-CAT score included several cancer-related factors (i.e. hormonal therapy, time since diagnosis, central catheter line, and advancement of cancer) and patient-related factors (i.e. comorbidities, hospitalization, history of VTE) in addition to a platelet count cut-off. The score displayed a good discriminatory power between high- and low risk for VTE in breast-, colorectal-, lung or ovarian cancer patients (58). In an external validation in lung cancer patients, the COMPASS-CAT score displayed a c-statistic of 0.85. The score was better at discriminating between high- and low risk than the KRS, Protecht and CONKO score (48). In the same year as the COMPASS-CAT, the ONCOTEV score was presented. The score included a KRS <2, history of VTE, metastatic disease and compression tumours (57), the score yield promising performance in the development study, but has not been externally validated. The next proposed RAM, the TiC-onco index, is based on the patients' clinical and genetic risk factors for VTE (59). The published paper display the RAM to perform better than the KRS (c-statistic of 0.73 vs. 0.58). No studies have externally validated the risk index, and might be due to panel is a commercial product not available for all laboratories.

One RAM created to a subtype of cancer has been introduced. Antic and colleagues presented the Throly score designed to predict thrombotic events (venous and arterial) for patients with lymphoma (56). The score showed promising predictive performance (PPV of 25.1% and NPV of 98.5%). However, no studies have externally validated the score.

In 2018, researchers behind the Vienna CATS score aimed to improve the score and make a model easy accessible to clinicians and proposed a nomogram including only cancer site and a D-dimer as a continuous parameter. The developed nomogram performed with a C-statistic of 0.68 when validating in an independent cohort, displaying a good ability to distinguish between high- and low risk of VTE in ambulatory cancer patients (60). The development and validation cohort used different arrays for measuring D-dimer, strengthening the generalizability. However, no further articles have validated the nomogram.

Across the identified RAMs and their validation studies there is a substantial difference in terms of studied populations, such as incidental VTE vs. symptomatic VTE, advancement of disease and follow-up time. This is possibly a strength when externally validating a RAM, as it represent a more real-world display of the performance of the score. However, heterogeneity between the development populations of the different RAMs, hampers the direct comparison between the proposed RAMs. Two studies comparing different RAMs in independent population aid in the direct evaluation. van Es and collegues compared the performance of the KRS, Vienna CATS, Protecht and CONKO in a population of ambulatory cancer patients and found the Vienna CATS and Protecht score superior to the KRS and CONKO score (51). Rupa-Matysek compared the KRS, Protecht, CONKO and COMPASS-CAT to a study of lung cancer patients and found the COMPASS-CAT to be the most accurate at predicting VTE.

Some studies included incidentally diagnosed VTE from routine CT scans during cancer-monitoring (44, 51, 53, 57). This could result in an overestimation of VTE not necessarily clinically relevant. Moreover, current guidelines do not recommend treatment of incidental VTE unless it is a proximal PE or present symptoms of VTE (62).

The complexity of identified RAMs vary, leading the availability to vary accordingly. The most complex model is the TiC-onco. And the model with fewest parameters are the Vienna nomogram, however, since D-dimer on a continuous scale is incorporated. A simple RAM is easier to implement into the clinic, but may compromise the performance. A complex RAM that require more effort calculating from the clinician may be harder to implement but actually have better performance.

In clinical medicine the usage of RAMs is frequent, and essential. In a setting where a doctor is one-on-one with a patient, knowledge about which parameters or traits to base a

decision on (e.g. start primary thrombophylaxis) is left mostly to the subjective opinion of the treating physician. RAMs provide standardized measurement to aid clinicians in the decision making process, hence, optimize treatment and create a more evidence based practice overall. Therefore, the amount of publications regarding RAMs have increased exponentially throughout the recent years (63). However, in a systematic review evaluating the quality of published prognostic studies, the vast majority did not follow current methodological recommendations (64). This is reflected in our findings, in which many studies are of retrospective design and majority of studies report on relative risks as opposed to the preferred reporting of absolute risk in prognostic studies. Moreover, validation of a RAM was not primary aim of several identified studies, making the performance measurement of the RAMs suboptimal.

The future prospective for VTE-RAMs in ambulatory cancer patients is uncertain. The most validated model is the KRS, several studies have raised concerns since the majority of events occur in the intermediate risk group. However, two recently completed randomized control trials (identifiers: 02555878 and 02047765) to determine efficacy of DOACs (direct-acting oral anticoagulants) in cancer patients, used the KRS at a cut-off of ≥2 as inclusion criteria. So hopefully findings from this will be published in the near future, expanding the knowledge on the KRS. Nonetheless, one might think a good approach could be to introduce RAMs for all subtypes of cancer. This would require tremendously amount of research as there are over 100 different cancer sites, and all would require external validation and subsequent clinical testing. If instead, more complex scores are implemented, development of automatic calculation of risk is one way this may be feasible in a clinical setting.

The fundamental challenge in cancer-related thrombosis, is the increased risk of major bleeding complications that follow treatment with thromboprophylaxis. Of the RAMs developed to determine risk of cancer-related VTE, none of them account for risk of major bleeding. In the future, the bleeding-risk could be incorporated to the risk score by subtracting the total score if identified predictors of such are present. Another method is by creating an additional risk score for bleeding risk and evaluating the risk for adverse outcomes against the risk of VTE. However, in order to do so, more research is needed to determine the benefit-to-harm ratio.

A strength of the current thesis is the systematic approach in two different databases, complemented with a free-text search to capture not yet indexed articles. The selection process relied solely on one person. However, in order to limit potential selection bias, inclusion- and exclusions criteria was predefined. Another possible limitation is that due to the large amount of research on the topic that is cancer-related thrombosis, RAMs could be investigated in sub-analysis and thereby overlooked. To decrease the possibility of this, a cross-reference screen on included articles was done.

5. Conclusion

The proportion of cancer-related VTE events is highest within the first months after diagnosis and initiation of anti-cancer treatment. Several risk assessment models were identified in the search, where the first RAM launched (i.e the Khorana risk score), had been most thoroughly validated, while other had not been validated at all. A problem with prognostic research in this population is the heterogeneity of cancer patients, and finding a prediction model suitable for is therefore challenging. Continuing efforts is needed to determine the risk of major bleeding on anticoagulant therapy in order to account for this in cancer patients. Of the identified RAMs, several show promising result, but none have been explored in a controlled clinical prospective setting and therefore more research is necessary to determine the clinical feasibility of these models.

6. References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
3. Soerjomataram I, Lortet-Tieulent J, Parkin DM, Ferlay J, Mathers C, Forman D, et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. Lancet. 2012;380(9856):1840-50.
4. Norway CRo. Cancer in Norway 2017 - Cancer incidence, mortality, survival and prevalence in Norway. Oslo; 2018.
5. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100(1):57-70.
6. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74.
7. Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. Am J Epidemiol. 2005;162(10):975-82.
8. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med. 2004;117(1):19-25.
9. Raskob GE, Angchaisuksiri P, Blanco AN, Buller H, Gallus A, Hunt BJ, et al. Thrombosis: a major contributor to global disease burden. Arterioscler Thromb Vasc Biol. 2014;34(11):2363-71.
10. Rosendaal FR. Risk factors for venous thrombotic disease. Thromb Haemost. 1999;82(2):610-9.
11. Bovill EG, van der Vliet A. Venous valvular stasis-associated hypoxia and thrombosis: what is the link? Annu Rev Physiol. 2011;73:527-45.
12. Braekkan SK, Borch KH, Mathiesen EB, Njolstad I, Wilsgaard T, Hansen JB. Body height and risk of venous thromboembolism: The Tromso Study. Am J Epidemiol. 2010;171(10):1109-15.
13. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. Br J Cancer. 2010;102 Suppl 1:S2-9.
14. Agnelli G, Verso M. Thrombosis and cancer: clinical relevance of a dangerous liaison. Haematologica. 2005;90(2):154-6.
15. Noboa S, Mottier D, Oger E, Group E-GS. Estimation of a potentially preventable fraction of venous thromboembolism: a community-based prospective study. J Thromb Haemost. 2006;4(12):2720-2.
16. Cronin-Fenton DP, Sondergaard F, Pedersen LA, Fryzek JP, Cetin K, Acquavella J, et al. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006. Br J Cancer. 2010;103(7):947-53.
17. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005;293(6):715-22.
18. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med. 2006;166(4):458-64.

19. Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. Cancer. 2013;119(3):648-55.
20. Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine (Baltimore). 1999;78(5):285-91.
21. Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. The New England journal of medicine. 2000;343(25):1846-50.
22. Spencer FA, Lessard D, Emery C, Reed G, Goldberg RJ. Venous thromboembolism in the outpatient setting. Arch Intern Med. 2007;167(14):1471-5.
23. Connolly GC, Phipps RP, Francis CW. Platelets and cancer-associated thrombosis. Semin Oncol. 2014;41(3):302-10.
24. Del Conde I, Bharwani LD, Dietzen DJ, Pendurthi U, Thiagarajan P, Lopez JA. Microvesicle-associated tissue factor and Trousseau's syndrome. J Thromb Haemost. 2007;5(1):70-4.
25. Rao LV. Tissue factor as a tumor procoagulant. Cancer Metastasis Rev. 1992;11(3-4):249-66.
26. Callander NS, Varki N, Rao LV. Immunohistochemical identification of tissue factor in solid tumors. Cancer. 1992;70(5):1194-201.
27. Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: biological and clinical aspects. J Thromb Haemost. 2013;11(2):223-33.
28. Lima LG, Monteiro RQ. Activation of blood coagulation in cancer: implications for tumour progression. Biosci Rep. 2013;33(5).
29. Di Nisio M, Porreca E, Ferrante N, Otten HM, Cuccurullo F, Rutjes AW. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database Syst Rev. 2012(2):CD008500.
30. Di Nisio M, Porreca E, Candeloro M, De Tursi M, Russi I, Rutjes AW. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database Syst Rev. 2016;12:CD008500.
31. Grobbee DE, Hoes AW. Clinical Epidemiology: Principles, Methods, and Applications for Clinical Research. Sudbury, MA: Jones and Bartlett; 2009.
32. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? BMJ. 2009;338:b375.
33. Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: Developing a prognostic model. BMJ. 2009;338:b604.
34. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. BMJ. 2009;338:b605.
35. Bhopal R. Consepts of epidemiology. Oxford, United kingdom: Oxford University Press; 2008. 480 p.
36. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
37. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.

38. Goldet G, Howick J. Understanding GRADE: an introduction. J Evid Based Med. 2013;6(1):50-4.
39. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111(10):4902-7.
40. Mandala M, Clerici M, Corradino I, Vitalini C, Colombini S, Torri V, et al. Incidence, risk factors and clinical implications of venous thromboembolism in cancer patients treated within the context of phase I studies: the 'SENDO experience'. Annals of oncology : official journal of the European Society for Medical Oncology. 2012;23(6):1416-21.
41. Kim SY, Burns ZT, Henry DH. The assessment of thrombotic risk using a predictive model in metastatic cancer patients undergoing first-line therapy. Thromb Res. 2012;130(6):967-70.
42. Panizo E, Alfonso A, Garcia-Mouriz A, Lopez-Picazo JM, Gil-Bazo I, Hermida J, et al. Factors influencing the use of thromboprophylaxis in cancer outpatients in clinical practice: A prospective study. Thromb Res. 2015;136(6):1145-8.
43. Lustig DB, Rodriguez R, Wells PS. Implementation and validation of a risk stratification method at The Ottawa Hospital to guide thromboprophylaxis in ambulatory cancer patients at intermediate-high risk for venous thrombosis. Thromb Res. 2015;136(6):1099-102.
44. van Es N, Franke VF, Middeldorp S, Wilmink JW, Buller HR. The Khorana score for the prediction of venous thromboembolism in patients with pancreatic cancer. Thromb Res. 2017;150:30-2.
45. Kruger S, Haas M, Burkl C, Goehring P, Kleespies A, Roeder F, et al. Incidence, outcome and risk stratification tools for venous thromboembolism in advanced pancreatic cancer - A retrospective cohort study. Thromb Res. 2017;157:9-15.
46. Fuentes HE, Paz LH, Wang Y, Oramas DM, Simons CR, Tafur AJ. Performance of Current Thromboembolism Risk Assessment Tools in Patients With Gastric Cancer and Validity After First Treatment. Clin Appl Thromb Hemost. 2018;24(5):790-6.
47. Mansfield AS, Tafur AJ, Wang CE, Kourelis TV, Wysokinska EM, Yang P. Predictors of active cancer thromboembolic outcomes: validation of the Khorana score among patients with lung cancer. J Thromb Haemost. 2016;14(9):1773-8.
48. Rupa-Matysek J, Lembicz M, Rogowska EK, Gil L, Komarnicki M, Batura-Gabryel H. Evaluation of risk factors and assessment models for predicting venous thromboembolism in lung cancer patients. Med Oncol. 2018;35(5):63.
49. Kuderer NM, Poniewierski MS, Culakova E, Lyman GH, Khorana AA, Pabinger I, et al. Predictors of Venous Thromboembolism and Early Mortality in Lung Cancer: Results from a Global Prospective Study (CANTARISK). Oncologist. 2018;23(2):247-55.
50. Patell R, Rybicki L, McCrae KR, Khorana AA. Predicting risk of venous thromboembolism in hospitalized cancer patients: Utility of a risk assessment tool. Am J Hematol. 2017;92(6):501-7.
51. van Es N, Di Nisio M, Cesarman G, Kleinjan A, Otten HM, Mahe I, et al. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. Haematologica. 2017;102(9):1494-501.
52. Mulder FI, Candeloro M, Kamphuisen PW, Di Nisio M, Bossuyt PM, Guman N, et al. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. Haematologica. 2019.
53. Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, Simanek R, et al. Prediction of venous thromboembolism in cancer patients. Blood. 2010;116(24):5377-82.

54. Verso M, Agnelli G, Barni S, Gasparini G, LaBianca R. A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. Intern. 2012;7(3):291-2.
55. Pelzer U, Sinn M, Stieler J, Riess H. [Primary pharmacological prevention of thromboembolic events in ambulatory patients with advanced pancreatic cancer treated with chemotherapy?]. Dtsch Med Wochenschr. 2013;138(41):2084-8.
56. Antic D, Milic N, Nikolovski S, Todorovic M, Bila J, Djurdjevic P, et al. Development and validation of multivariable predictive model for thromboembolic events in lymphoma patients. Am J Hematol. 2016;91(10):1014-9.
57. Cella CA, Di Minno G, Carlomagno C, Arcopinto M, Cerbone AM, Matano E, et al. Preventing Venous Thromboembolism in Ambulatory Cancer Patients: The ONKOTEV Study. Oncologist. 2017;22(5):601-8.
58. Gerotziafas GT, Taher A, Abdel-Razeq H, AboElnazar E, Spyropoulos AC, El Shemmari S, et al. A Predictive Score for Thrombosis Associated with Breast, Colorectal, Lung, or Ovarian Cancer: The Prospective COMPASS-Cancer-Associated Thrombosis Study. Oncologist. 2017;22(10):1222-31.
59. Martin AJM, Ortega I, Font C, Pachon V, Castellon V, Martinez-Marin V, et al. Multivariable clinical-genetic risk model for predicting venous thromboembolic events in patients with cancer. Br J Cancer. 2018;118(8):1056-61.
60. Pabinger I, van Es N, Heinze G, Posch F, Riedl J, Reitter EM, et al. A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts. Lancet Haematol. 2018;5(7):e289-e98.
61. Khorana AA, Francis CW, Culakova E, Lyman GH. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. Cancer. 2005;104(12):2822-9.
62. Di Nisio M, Lee AY, Carrier M, Liebman HA, Khorana AA, Subcommittee on H, et al. Diagnosis and treatment of incidental venous thromboembolism in cancer patients: guidance from the SSC of the ISTH. J Thromb Haemost. 2015;13(5):880-3.
63. Steyerberg E. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. Springer, editor. New York: Springer-Verlag; 2009. 500 p.
64. Bouwmeester W, Zuithoff NP, Mallett S, Geerlings MI, Vergouwe Y, Steyerberg EW, et al. Reporting and methods in clinical prediction research: a systematic review. PLoS Med. 2012;9(5):1-12.

7. Tables

Table 1: Articles on the Khorana risk score for predicting cancer-related venous thromboembolism

Author, year (citation)	Study design	Cancer type	Study popul-ation (n)	Study selection	Symptom-atic VTE only*	Median follow up	Percentage of VTE events by risk categories (with points of Khorana risk score)	Reported performance of the Khorana risk score
Khorana et al., 2008 (39)	Prospective cohort Divided in two with one development (n= and one validation cohort	Various	2701 1365	Cancer patients initiating new chemotherapy	Yes	2.4 months 2.4 months	High risk: 7.1% Intermediate risk:1.8% Low risk:0.8% High risk (≥3): 6.7% Intermediate risk(12): 2.0% Low risk (0):0.3%	<u>At 6 months using a cut-off at ≥ 3 points:</u> Sensitivity 40.0% Specificity 88.0% PPV 7.1% NPV 98.5% C-statistic of 0.7 <u>At 6 months using a cut-off at ≥ 3 points:</u> Sensitivity 35.7% Specificity 89.6% PPV 6.7% NPV 98.5% C-statistic of 0.7
Ay et al., 2010 (53)	Prospective cohort	Brain, breast, GI-, pancreas, kidney, prostate and haematological cancers	819	Incident cancer diagnoses and relapse of disease, to be initiating chemotherapy	No	22 months	High risk(≥3): 17.7% Intermediate risk (2): 9.6% Intermediate/low risk(1): 3.8% Low risk (0): 1.5%	<u>At 6 months with cut-off at ≥ 3 points:</u> Sensitivity 31.9% Specificity 91.9% PPV 22.1% NPV 94.9% C-statistic not reported.
Verso et al., 2012 (54)	Prospective (RCT, multicentre study, Italy)	Lung, GI-, pancreatic, breast ovarian and head/neck cancers	378	Patients receiving chemotherapy for metastatic or locally advanced solid cancer	Yes	NA	High risk (≥3): 11.1% Intermediate-low risk (0-2): 3.0%	<u>Cut off at ≥ 3 points:</u> Sensitivity 33.3% Specificity 89.1% PPV 11.1% NPV 97.0%
Mandalà et al., 2012 (40)	Prospective	Various	1412	Only patients with advanced cancer and treated with experimental antitumor agents	NA	2 months	High risk(≥3): 12.9% Intermediate risk: 4.8% Low risk: 1.5%	C-statistic 0.65

Kim et al., 2012 (41)	Retrospective	Various	90	Patients with metastatic disease about to initiate chemotherapy	Not specified	19 months	High risk(≥3): 37% Intermediate risk(1-2): 20% Low risk(0): 24%	NA
Lustig et al., 2015 (43)	Prospective observation cohort (single centre study, Canada)	Various	580	Glioma, bladder, lung, testicular, gynaecological, pancreatic, lymphoma, and relapse after remission	Yes	3.0 months	High/intermediate risk(≥2):11% Low risk (0-1): 4%	NA
Panizo et al., 2015 (42)	Prospective (Single centre study, Spain)	Various	1108	Solid- or haematological cancer patients receiving systemic antineoplastic treatment	Yes	3.0 months	High risk: 10.6% Intermediate risk: 6.3% Low risk: 3.4%	NA
Van Es et al., 2017 (44)	Retrospective (single centre, the Netherlands)	Pancreatic	178		No	7.7 months	High risk (≥3): 9.5% Intermediate risk (2): 8.2% *(All patients got 2 point due to pancreatic cancer)*	NA
Mansfield et al., 2016 (47)	Prospective	Lung	719	All lung cancer patients within a catchment of a treatment clinic	No	15.2 months	High risk(≥3): 6.2% Intermediate risk(1-2): 6.3% *(All patients got 1 point due to lung cancer)*	NA
Cella et al., 2017 (57)	Prospective (Multinational cohort study, Italy and Germany)	Solid malignant tumours	843	Patients with active cancer	No	8.3 months	<u>At 12 months:</u> High risk (≥3): 21.7% Intermediate risk (1-2): 9.2% Low risk (0): 8.8%	<u>C-statistic:</u> At 3 months 0.58 At 6 months 0.59 At 12 months 0.58
Van Es et al., 2017 (51)	Prospective (multinational study)	Various	876	Patients with stage III and IV solid tumours	No	6 months	High risk: 6.5%	<u>At 6 months:</u> 0.50 (95% CI 0.42-0.57)
Patell et al., 2017 (50)	Retrospective (Single centre, USA)	Various	2780	Inpatients, the vast majority was admitted due to chemotherapy, infection, GI-symptoms	Yes	Unknown	High risk (≥3): 6% Intermediate risk(1-2): 4%	NA
Kruger et al., 2017 (45)	Retrospective	Pancreatic cancer	172	Outpatients with advanced malignancy receiving palliative chemotherapy	No	9.2 months	High risk (≥3):19% Intermediate risk (2): 12% *(All patients 2 at least points due to pancreatic cancer)*	NA
Fuentes et al., 2018 (46)	Retrospective	Gastric cancer	112	All gastric patients treated within a treatment facility	No	21.3 months	High risk: 15% Intermediate risk: 9.3%	Sensitivity 69% Specificity 49% PPV 15% NPV 88%

Kuderer et al., 2018 (49)	Prospective	Lung cancer	1980	Patients with lung cancer initiating new therapy	No	5 days	High risk(≥3): 5.4% Intermediate(2): 6.5% Low(1): 6.4%	NA
Muñoz-Martín et al., 2018 (59)	Prospective	Various	391	Recent diagnosis and eligible for systemic outpatient chemotherapy	Yes	6.0 months	High risk (≥3): 21% Intermediate (1-2): 19.8% Low risk(0): 12.9%	<u>At 6 months:</u> Sensitivity 22.5% Specificity 81.8% PPV 21.6% NPV 82.5% C-statistic of 0.58
Rupa-Maytsek et al., 2018 (48)	Retrospective (Single centre, Poland)	Lung cancer	118	Outpatients receiving treatment for lung cancer	Yes	2.5 months	High risk (≥3) :13% Low/intermediate risk (≤2): 17.5%	At 6 months with cut-off at ≥3: Sensitivity 10.0% Specificity 100.0% PPV 17.0 % NPV 83.0% C-statistic 0.81%
Pabinger et al., 2018 (60)	*Development*: Prospective (Single centre study, Austria)	*Development*: Solid cancers and lymphoma	1432	*Development*: CATS[1] Newly diagnosed or relapsed after complete/partial remission solid cancer patients	Yes	*Development*: 3.0 months	Not reported	<u>C-statistics at 6 months:</u> CATS 0.61
	Validation: Prospective (Multinational study, the Netherlands, France, Italy and Mexico)	*Validation*: Advanced solid cancers	822	*Validation*: MICA[2] Ambulatory solid cancer patients with advanced disease	No	*Validation*: 3.0 months	Not reported	<u>C-statistics at 6 months:</u> MICA 0.56
Mulder et al., 2019 (52)	Meta-analysis	Various	34 555	Ambulatory cancer patients	No	2-79 months	High risk(≥3): 11.0% Intermediate risk(1-2): 6.6% Low risk(0):5.1%	Not reported

NA: Not avalible; + [1] Vienna CATS: Vienna Cancer and Thrombosis Study; [2]MICA: Multinational Cohort Study to Identify Cancer Patients at High Risk of Venous Thromboembolism

Table 2: Articles on the Vienna CATS score for predicting cancer-related venous thromboembolism

Author, year (Citation)	Study design	Cancer type	Study popu-lation (n)	Study selection	Symptom-atic VTE only[+]	Median follow up	Percentage of VTE events by risk categories (point of Vienna CATS risk score)	Reported performance of the Vienna CATS risk score
Ay, 2010 (53)	Prospective cohort	Brain, breast, GI-, pancreas, kidney, prostate and haematological cancers	819	Incident cancer patients and relapse of disease, to be initiating chemotherapy	No	22 months	High risk(≥3): 17.7% Intermediate risk (2): 9.6% Intermediate/low risk(1): 3.8% Low risk (0): 1.5%	<u>At 6 months with cut-off at ≥ 5 points:</u> Sensitivity 19.1% Specificity 98.2% PPV 42.9% NPV 94.4% C-statistic not reported.
Van Es, 2017 (51)	Prospective (multinational study)	Various	876	Patients with stage III and IV solid tumours	No	2 months	High risk (≥3): 8.4% Low risk: NA	<u>At 6 months with cut-off at C statistic ≥ 3 points:</u> 0.57 (95% CI, 0.48-0.66)

Table 3: Articles on the Protecht risk score for predicting cancer-related venous thromboembolism

Author, year (citation)	Study design	Cancer type	Study popu-lation (n)	Study selection	Symptom-atic VTE only*	Median follow up	Percentage of VTE events by risk categories (point of Protect score)	Performance of the Protecht risk assessment model
Verso et al., 2012 (54)	Prospective (RCT, multicentre study, Italy)	Lung, GI-, pancreatic, breast ovarian and head/neck cancers	378	Patients receiving chemotherapy for metastatic or locally advanced solid cancer	Yes	NA	High risk (≥3): 8.0% Low risk(0-2): 2%	NA
Van Es et al., 2017 (51)	Prospective (multinational study)	Various	876	Patients with stage III and IV solid tumours	No	2 months	High risk (≥3): 9.5% Low risk: NA	Time dependent at 3 months: C-statistic 0.54 (95% CI, 0.45-0.63)
Rupa-Maytsek et al., 2018 (48)	Retrospective (Single centre, Poland)	Lung cancer	118	Outpatients receiving treatment for lung cancer	Yes	2.5 months	High risk (≥3): 17.7% Low/intermediate risk: 16.0%	At 6 months with cut-off at ≥ 3 points: Sensitivity 20.0% Specificity 78.0% PPV 18% NPV 84% C-statistic 0.51

Abbreviations: NA – not available

Table 4: Articles on the CONKO risk score for predicting cancer-related venous thromboembolism

Author, year (citation)	Study design	Cancer type	Study popul-ation (n)	Study selection	Symptom-atic VTE only*	Median follow up	Percentage of VTE events by risk categories (point of Khorana risk score)	Performance of the CONKO risk assessment model
*Pelzer, 2013 (55)	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Van Es, 2017 (51)	Prospective (multinational study)	Various	876	Patients with stage III and IV solid tumours	No	2 months	High risk (≥3): 5.2% Low risk: NA	Time dependent at 3 months C-statistic 0.5 (95% CI, 0.42-0.57)
Rupa-Maytsek et al., 2018 (48)	Retrospective (Single centre, Poland)	Lung	118	Outpatients receiving treatment for lung cancer	Yes	2.5 months	High risk (≥3): 17.7% Low/intermediate risk: 16.0%	At 6 months with cut-off at ≥ 3 points: Sensitivity 20.0% Specificity 78.0% PPV 18% NPV 84% C-statistic 0.51

* Original article not available in English. Abbreviations: NA - Not available

Table 5: Articles on the ThroLy risk score for predicting cancer-related thromboembolism in lymphoma patients

Author, year (citation)	Study design	Cancer type	Study popul-ation (n)	Study selection	Symptom-atic VTE only*	Median follow up	Percentage of VTE events by risk categories (point of ThroLy risk score)	Performance of the ThroLy risk assessment model
Antic et al., 2016 (56)	Prospective cohort (Single centre, Serbia)	Lymphoma	1236 584	Patients with newly diagnosed and relapsed lymphoma patients receiving, a minimum 1 cycle of chemotherapy	Yes	NA	Development: High risk (≥4): 65.2% Intermediate risk (2-3): 19.8% Low risk (0-1): 1.5% Validation: NA	Development: PPV 65.2% C-statistic 0.88 Validation: Sensitivity 64.7% Specificity: 90.2% PPV 28.9% NPV: 97.6% C-statistic 0.86

NA: not available

Table 6: Articles on the ONKOTEV risk score for predicting cancer-related venous thromboembolism

Author, year (citation)	Study design	Cancer type	Study population (n)	Study selection	Symptomatic VTE only*	Median follow up	Percentage of VTE events by risk categories (point of Khorana risk score)	Performance
Cella et al., 2017 (57)	Prospective (Multinational cohort study, Italy and Germany)	Solid malignant tumours	843	Patients with active cancer	No	8.3 months	At 12 months: Score ≥2: 33.9% Score 2: 19.4% Score 1: 9.7% Score 0: 3.7%	At 3 months: C-statistic 0.72 At 6 months: C-statistic 0.75 At 12 months: C statistic 0.70

Table 7: Articles on the COMPASS-CAT risk score for predicting cancer-related venous thromboembolism

Author, year (citation)	Study design	Cancer type	Study population (n)	Study selection	Symptomatic VTE only*	Median follow up	Percentage of VTE events by risk categories (point of COMPASS-CAT risk score)	Performance of the COMPASS-CAT risk assessment model
Gerotziafas et al., 2017 (58)	Prospective (multinational cohort, France, Lebanon, Jordan, Saudi Arabia, Kuwait)	Breast-, colon-, lung- and ovarian cancer	1023	Solid cancer patients about to initiate chemotherapy	Yes	NA	High risk (≥7): 13.3% Low/intermediate risk (0-6): 1.7%	At a cut-off at ≥7 at 6 months: Sensitivity 88% Specificity 52% PPV NA NPV 98%
Rupa-Maytsek et al., 2018 (48)	Retrospective (Single centre, Poland)	Lung	118	Outpatients receiving treatment for lung cancer	Yes	2.5 months	High risk (≥7): 23.8% Low/intermediate risk (0-6): 0%	Sensitivity 100% Specificity 35% PPV 24% NPV 100% C-statistic 0.89

NA: not available

Table 8: Articles on the TiC-Onco risk score for predicting cancer-related venous thromboembolism

Author, year (citation)	Study design	Cancer type	Study popul-ation (n)	Study selection	Symptom-atic VTE only*	Median follow up	Percentage of VTE events by risk categories (point of Khorana risk score)	Performance of the TiC-onco risk assessment model
Muñoz-Martín et al., 2018 (59)	Prospective	Various	391	Recent diagnosis and eligible for systemic outpatient chemotherapy	Yes	NA	High risk: 36.8% Non-high risk: 12.2% Moderate risk: 18.3% Low risk: 5.6%	At 6 months: Sensitivity 85.9% (95% CI 77.8-94.0) Specificity 49.1% (95% CI 43.6-54.5) NPV 94.1% (95% CI 90.4-97.6) PPV 27.3% (95% CI 21.4-33.1) C-statistic 0.73 (95% CI 0.67-0.79)

NA: not available

Table 9: Articles on the Vienna nomogram for predicting cancer-related venous thromboembolism

Author, year (citation)	Study design	Cancer type	Study popul-ation (n)	Study selection	Symptom-atic VTE only*	Median follow up	Percentage of VTE events by risk categories (point of Vienna nomogram risk score)	Performance of the Vienna nomogram
Pabinger et al., 2018 (60)	*Development*: Prospective (Single centre study, Austria)	*Development*: Solid cancers and lymphoma	*Development:* 1432	*Development*: CATS[1] Newly diagnosed or relapsed after complete/partial remission solid cancer patients	Yes	*Development*: 3.0 months	NA	At six months with a 10% probability cut-off: Sensitivity 33% (95% CI 23-47) Specificity 84% (95% CI 83-87) NPV 95% (95% CI 94-96) PPV 12% (95% CI 8-16) C-statistic 0.66 (95%CI 0.36-0.67)
	Validation: Prospective (Multinational study, the Netherlands, France, Italy and Mexico)	*Validation*: Advanced solid cancers	*Validation*: 822	*Validation*: MICA[2] Ambulatory solid cancer patients with advanced disease	No	*Validation*: 3.0 months		At 15% cut-off for predicting 6-month risk of VTE Sensitivity 8% (95% CI 2-20) Specificity 99% (95% CI 98-99) NPV 95% (95% CI 93-96) PPV 29% (95% CI 8-58) C-statistic 0.68 (95% CI 0.62-0.74)

[1] Vienna CATS: Vienna Cancer and Thrombosis Study: including newly diagnosed or relapsed after complete/partial remission solid cancer patients; [2]MICA: Multinational Cohort Study to Identify Cancer Patients at High Risk of Venous Thromboembolism

Table 10. The Khorana risk score (39)

Characteristic	Risk score
Site of cancer	
Very high risk (stomach, pancres)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Platelet count ≥ 350 x 10^9/L	1
Haemoglobin level ≤100 g/L or red cell growth factors	1
Leucocyte count ≥ 11 x 10^9/L	1
≥BMI 35 kg/m^2	1
Maximum total	7

Abbreviations: BMI-Body mass index

Table 11. The Vienna CATS score (53)

Characteristic	Risk score
Site of cancer	
Very high risk	2
High risk	1
Platelet count ≥ 350 x 10^9/L	1
Haemoglobin level ≤100 g/L or red cell growth factors	1
Leucocyte count ≥ 11 x 10^9/L	1
≥BMI 35 kg/m^2	1
D-Dimer	1
P-selectin	1
Maximum total	9

Abbreviations: BMI-Body mass index

Table 12. The Protecht score (54)

Characteristic	Risk score
Site of cancer	
Very high risk	2
High risk	1
Platelet count ≥ 350 x 10^9/L	1
Haemoglobin level ≤100 g/L or red cell growth factors	1
Leucocyte count ≥ 11 x 10^9/L	1
≥BMI 35 kg/m^2	1
Chemotherapy (Platinum-or gemcitabine-based)	1
Maximum total	8

Abbreviations: BMI-Body mass index

Table 13: The CONKO score (55)

Characteristic	Risk score
Site of cancer	
Very high risk	2
High risk	1
Platelet count ≥ 350 x 10^9/L	1
Haemoglobin level ≤100 g/L or red cell growth factors	1
Leucocyte count ≥ 11 x 10^9/L	1
WHO performance status ≥2	1
Maximum total	7

Abbreviations: BMI-Body mass index; WHO-World health organization

Table 14: The ThroLy risk (56)

Characteristic	Risk score
Previous VTE/AMI/Stroke	2
Reduced mobility (ECOG 2-4)	1
Obesity (BMI >30 kg/m^2)	2
Extranodal localization	1
Mediastinal involvement	2
Neutrophils <1 x 10^9/L	1
Haemoglobin level <100 g/l	1
Maximum total	10

Abbreviations: BMI - Body mass index

Table 15. The ONKOTEV score (57)

Characteristic	Risk score
Khorana risk score >2	1
Previous venous thromboembolism	1
Metastatic disease	1
Vascular/lymphatic macroscopic compression	1
Maximum total	4

Table 16. The Compass-CAT score (58)

Characteristic	Risk score
Cancer-related factors	
Antihormonal therapy for women with HR+[+] breast cancer or on anthracycline treatment	6
Time since diagnosis ≤ 6 months	4
CVC*	3
Advances stage of cancer	2
Predisposing risk factors	
Cardiovascular risk factors (composed by at least two of the following predictors: personal history of peripheral artery disease, ischemic stroke, coronary artery disease, hypertension, hyperlipidaemia, diabetes, obesity)	5
Recent hospitalization for acute medical illness	5
Personal history of VTE	1
Biomarkers	
Platelet count ≥350x10^9/L	2
Total	28

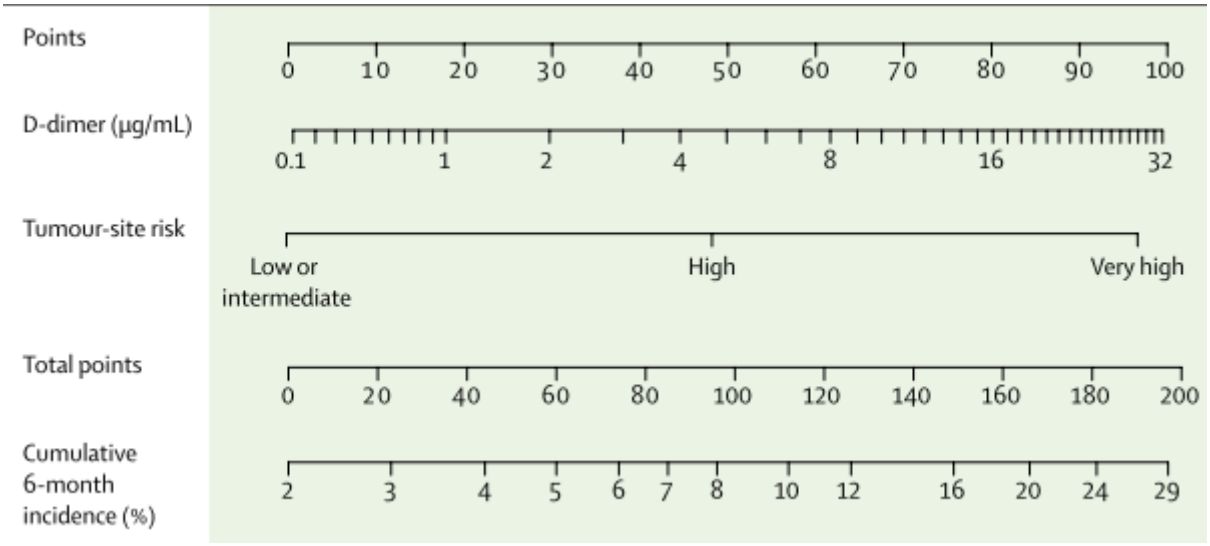
[+]HR+ hormonal receptor positive; *CVC; central venous catheter

Table 17: The Tic-Onco risk score (59)

Variable	p-value
Genetic risk score	0.0049
BMI>25	0.0658
Family history	0.1076
Primary tumour site	
High risk	0.3483
VHR	0.0033
Tumour	0.0003
Stage	
Genetic risk score	
Rs2232698	0.1460
Rs6025	0.2064
Rs5985	0.2003
Rs4524	0.0396

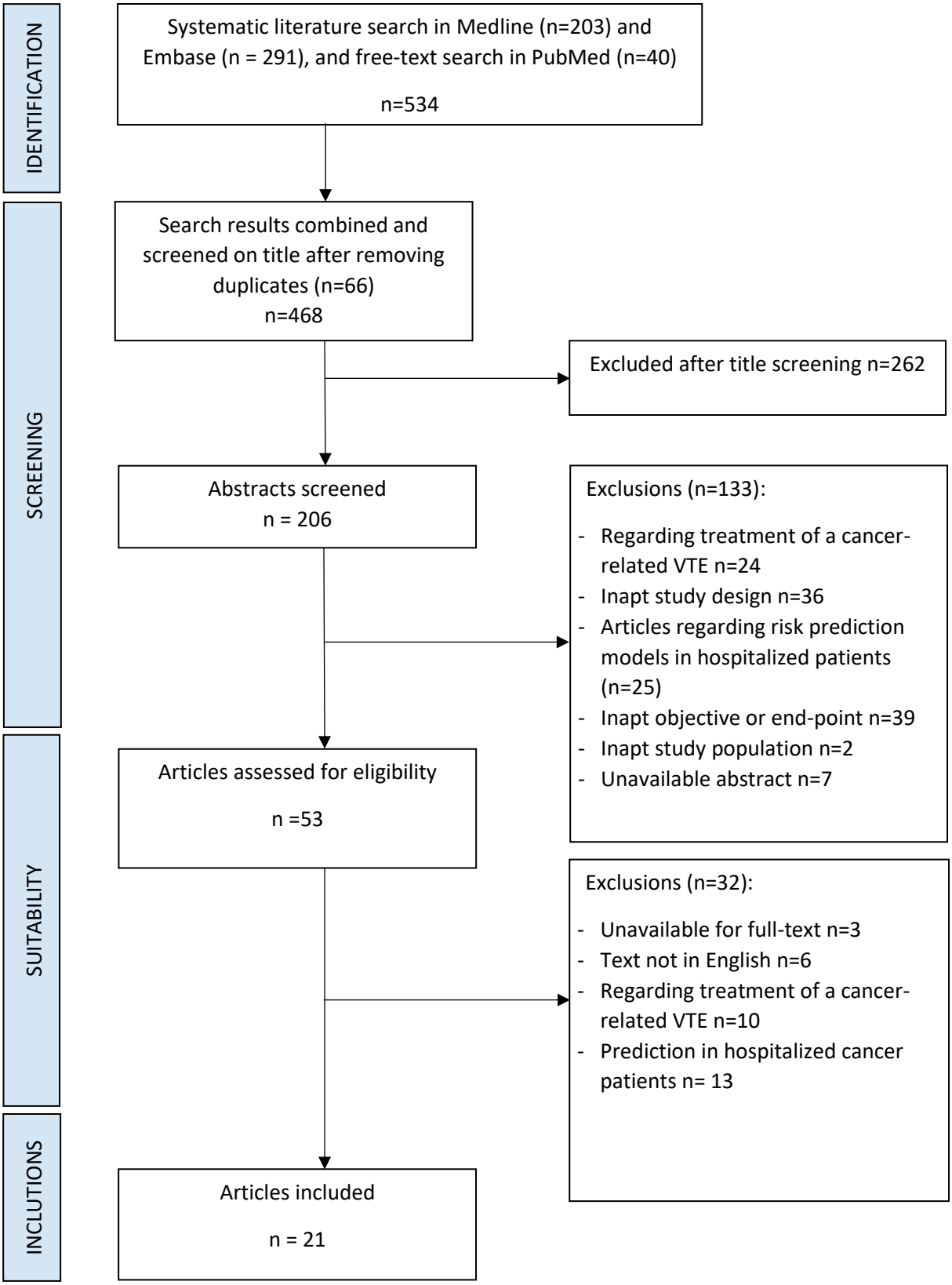
8. Figures

Figure 1: The CATS Nomogram for predicting the 6 month risk of venous thromboembolism. (60)



Very high risk cancer sites: Stomach, pancreas; **High risk cancer sites**: Lung, colorectal, lymphoma, genitourinary (excluding prostate), gynaecologic (excluding breast, oesophageal); **Low/intermediate risk cancer sites**: Breast and prostate

Figure 2. Modified PRISMA flow chart displaying the study selection for relevant articles regarding risk stratification models of VTE in cancer.



9. Appendix

Supplementary table 1. Systematic search in Ovid Medline.

#	Search	Text results	Type
1	Venous thromboembolism/co, ep, et, ge, pa, pc [complications, Epidemiology, Etiology, Genetics, Pathology, Prevention & control]	7244	Advanced
2	Thromboembolism/co, ep, et, ge, pa, pc [complications, Epidemiology, Etiology, Genetics, Pathology, Prevention & control]	16522	Advanced
3	Venous thrombosis/co, ep, et, ge, pa, pc [Complications, Epidemiology, Etiology, Genetics, Pathology, Prevention & control]	16564	Advanced
4	Thrombosis/co, ep, et, ge, pa, pc [complications, Epidemiology, Etiology, Genetics, Pathology, Prevention & control]	40593	Advanced
5	Neoplasms/co, di, ep, pa, th [Complications, Diagnosis, Epidemiology, Pathology, Therapy]	163026	Advanced
6	Cancer-associated thrombosis.ti,ab,kw.	288	Advanced
7	Risk assessment/ [Include all subheadings]	239572	Advanced
8	Decision Support Techniques/	18557	Advanced
9	Risk assessment model.ti,ab,kw.	801	Advanced
10	risk prediction scores.ti,ab,kw.	106	Advanced
11	comparison.m_titl.	326256	Advanced
12	"Predictive Value of Tests"/	189273	Advanced
13	1 or 2 or 3	38002	Advanced
14	5 or 6	163162	Advanced
15	7 or 8 or 9 or 10 or 11 or 12	743522	Advanced
16	13 and 14 and 15	239	Advanced
17	limit 16 to (english language and humans)	219	Advanced
18	limit 17 to yr="2008-current"	203	Advanced

Supplementary table 2. Systematic search in Ovid Embase.

#	Search	Text results	Type
1	Venous thromboembolism/co, dm, ep, et, pc [Complication, Disease Management, Epidemiology, Etiology, Prevention]	11400	Advanced
2	Thromboembolism/co, dm, ep, et, pc [Complication, Disease Management, Epidemiology, Etiology, Prevention]	22416	Advanced
3	vein thrombosis/co, dm, et, pc, si [Complication, Disease Management, Etiology, Prevention, Side Effect]	12074	Advanced
4	Thrombosis/co, dm, ep, et, pc, si [Complication, Disease Management, Epidemiology, Etiology, Prevention, Side Effect]	37599	Advanced
5	Neoplasm/co, di, dm, ep, si, th [Complication, Diagnosis, Disease Management, Epidemiology, Side Effect, Therapy]	39848	Advanced
6	Malignant neoplasm/co, di, dm, dt, ep, et, si, th [Complication, Diagnosis, Disease Management, Drug Therapy, Epidemiology, Etiology, Side Effect, Therapy]	6249	Advanced
7	Cancer patient/	294563	Advanced
8	Risk prediction model*.ti,ab,kw.	3090	Advanced
9	receiver operating characteristic/ or scoring system/	332786	Advanced
10	risk assessment/ or decision support system/	517429	Advanced
11	(Khorana score or Vienna CATS score or CONKO score or Protecht score or COMPASS-CAT or COMPASS-CAT or tic-onco).mp.	215	Advanced
12	(comparison or evaluation or validation).m_titl.	1088964	Advanced
13	1 or 2 or 3 or 4	79398	Advanced
14	5 or 6 or 7	339304	Advanced
15	8 or 9 or 10 or 11 or 12	1869998	Advanced
16	13 and 14 and 15	375	Advanced
17	limit 16 to (english language and humans)	359	Advanced
18	limit 17 to yr="2008 -Current"	291	Advanced

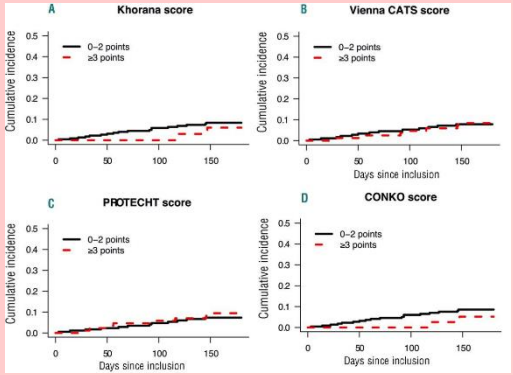
Supplementary table 3. Free-text search in PubMed

#	Search	Results	Type
1	Search (Venous thromboembolism[Title]) AND cancer[Title]	1007	Advanced
2	Search (Thromboembolism[Title]) AND Cancer[Title]	1140	Advanced
3	Search (Venous thrombosis[Title]) AND cancer[Title]	195	Advanced
4	Search ((((((((((Decision support techniques[Title/Abstract]) OR Risk prediction model*[Title/Abstract]) OR Risk assessment model*[Title/Abstract]) OR Risk assessment[[Title/Abstract]) OR Khorana score[Title/Abstract]) OR Vienna CATS score[Title/Abstract]) OR CONKO score[Title/Abstract]) OR Protecht score[Title/Abstract]) OR COMPASS-CAT[Title/Abstract]) OR tic-onco[Title/Abstract])	91	Advanced
5	Search (((((Decision support techniques[MeSH Major Topic]) OR Risk prediction mode[MeSH Major Topic]) OR Risk assessment model*[MeSH Major Topic]) OR Risk assessment[MeSH Major Topic]) OR ROC curve[MeSH Major Topic]) OR Adverse Outcome Pathways[MeSH Major Topic]	52597	Advanced
6	Search ((((((((((Decision support techniques[Title/Abstract]) OR Risk prediction model*[Title/Abstract]) OR Risk assessment model*[Title/Abstract]) OR Risk assessment[[Title/Abstract]) OR Khorana score[Title/Abstract]) OR Vienna CATS score[Title/Abstract]) OR CONKO score[Title/Abstract]) OR Protecht score[Title/Abstract]) OR COMPASS-CAT[Title/Abstract]) OR tic-onco[Title/Abstract])) OR ((((((Decision support techniques[MeSH Major Topic]) OR Risk prediction mode[MeSH Major Topic]) OR Risk assessment model*[MeSH Major Topic]) OR Risk assessment[MeSH Major Topic]) OR ROC curve[MeSH Major Topic]) OR Adverse Outcome Pathways[MeSH Major Topic])	52686	Advanced
7	Search (((((Venous thromboembolism[Title]) AND cancer[Title])) OR ((Thromboembolism[Title]) AND Cancer[Title])) OR ((Venous thrombosis[Title]) AND cancer[Title])) AND ((((((((((((Decision support techniques[Title/Abstract]) OR Risk prediction model*[Title/Abstract]) OR Risk assessment model*[Title/Abstract]) OR Risk assessment[[Title/Abstract]) OR Khorana score[Title/Abstract]) OR Vienna CATS score[Title/Abstract]) OR CONKO score[Title/Abstract]) OR Protecht score[Title/Abstract]) OR COMPASS-CAT[Title/Abstract]) OR tic-onco[Title/Abstract])) OR ((((((Decision support techniques[MeSH Major Topic]) OR Risk prediction mode[MeSH Major Topic]) OR Risk assessment model*[MeSH Major Topic]) OR Risk assessment[MeSH Major Topic]) OR ROC curve[MeSH Major Topic]) OR Adverse Outcome Pathways[MeSH Major Topic]))	40	Advanced

10. GRADE

<table>
<tr><td colspan="3">Reference: van Es N, Di Nisio M, Cesarman G, Kleinjan A, Otten HM, Mahe I, et al. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. Haematologica. 2017 Sep;102(9):1494-501.</td><td>GRADE
Quality of evidence: Moderate
Recommendations: N/A</td></tr>
<tr><td>Aim</td><td>Material and methods</td><td>Results</td><td>Discussion/Comments</td></tr>
<tr><td>To evaluate four clinical prediction scores for VTE in patients with advanced cancer receiving chemotherapy in a multinational cohort study.
Conclusion
Findings do not support the use of any of the examined scores to select patient for thrombophylaxis. Two of the prediction scores appeared to discriminate between high- and low-risk, but further improvements are needed before implication.
Country
Multinational
Year Data Collection
July 2008 – February 2016</td><td>Study design: Prospective cohort
Population: Patients with advanced cancer (stage III-IV) localized to lung, esophagus, colorectal, pancreatic, breast, prostate, gastric ovarian or bladder malignancy.
Eligibility: About to - or already initiated chemotherapy in the previous three months.
Exclusion criteria: Current prophylactic or therapeutic anticoagulation or adjuvant chemotherapy.
Outcome: DVT or PE during 6 months follow-up, incidental or symptomatic.
Statistical methods: Multiple imputation was applied to calculate the Khorana-, PROTECHT-, Vienna CATS- and CONKO score where data on one or more parameters.</td><td>53 (6.1%) patients developed VTE during 6 months follow-up. The area under the ROC curves ranged from 0.52 (95%CI: 0.47–0.58) for the Khorana score to 0.59 (95%CI: 0.52–0.66) for the PROTECHT score.

At the conventional positivity threshold of 3 points, the scores classified 13–34% of patients as high-risk; the 6-month incidence of venous thromboembolism in these patients ranged from 6.5% (95%CI: 2.8–12) for the Khorana score to 9.6% (95%CI: 6.6–13) for the PROTECHT score. High-risk patients had a significantly increased risk of venous thromboembolism when using the Vienna (subhazard ratio 1.7; 95%CI: 1.0–3.1) or PROTECHT (subhazard ratio 2.1; 95%CI: 1.2–3.6) scores.

 
</td><td>Parameters of hemoglobin levels, white blood cell count and platelet that was not associated with VTE in the sample, which may explained the overall poor discriminatory performance of the scores.
Only 3% was obese (BMI>35 included in CONKO), of whom none experienced a VTE.
Limitations
- Present study only access pre-chemotherapy hematological parameters as evaluated prediction scores was based on 260 patients, and for the group already started with antineoplastic treatment values was collected retrospective.
- Different assay for D-dimer than in the Vienna CATS score was utilized which can impact the dichotomous threshold in the score.
Strengths
- Multinational design limit possible single-center bias and strengthen the external validity.
- Large and prospective study including different tumor types limited to stage III and IV.
- Minimal loss to follow up and outcomes validated unrelated to score at baseline which minimize the potential for outcome bias.</td></tr>
</table>

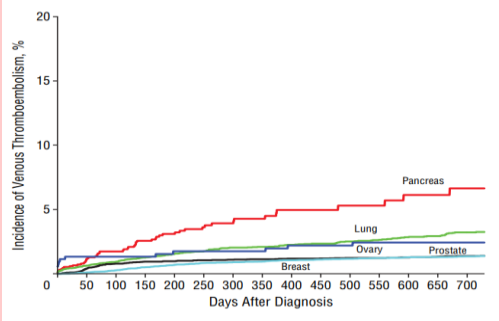
Reference: Mulder FI, Candeloro M, Kamphuisen PW, Di Nisio M, Bossuyt PM, Guman N, et al. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. Haematologica. 2019.			**GRADE**	
			Quality of evidence	Moderate/high
			Recommendations	N/A
Aim	**Material and methods**	**Results**	**Discussion/Comments**	
To evaluate the current evidence and present a collective current summary of evidence available on the Khorana risk score. **Conclusion** In current meta-analysis, Khorana risk score was found apt to stratify ambulatory cancer patient with high risk of VTE to thrombophylaxis, however the majority of events occurred in the non-high risk group. **Country** N/A **Year Data Collection** January 2008 to June 2018.	**Study design:** Meta-analysis **Identification of studies:** A systematic literary search was performed in Medline and Embase to identify studies incorporating the Khorana risk score to cancer patients. **Exposure**: Patients with cancer **Outcome**: Proportion of VTE (objectively confirmed, symptomatic or incidental) according to risk scores of the KRS. **Exclusions**: Derivation cohort of the Khorana risk score. Identified studies with shorter follow up than 6 months or missing end-point check-up at 6 months was excluded. **Statistical analyses** Identified studies was assessed for bias using standardized using the Quality in Prognosis Studies (QUIPS) tool. Tau-squared was calculated to assess between study heterogeneity. 6 months of follow-up was applied. Differences in subgroups was explored using chi-square test.	**Search results** After selection of 1879 crude search results, a total of articles and 8 abstracts including 55 cohort and 34555 ambulatory cancer patients. **Classification, incidence and distribution of VTE-event according to Khorana risk score** In pooled analysis, the distribution of cancer patients by Khorana risk score was 19% (n=6319), 64% (n=21172) and 17% (n=5614) in low, intermediate and high-risk group, respectively. At 6 months, the incidence of VTE according to KRS was 5.1% (95%CI 3.9-6.5) in the low risk group, 6.6% (95%CI 5.6-7.7) in the intermediate risk group and 11.0% (95%CI 8.8-13.8) in the high-risk group. Interestingly, the distribution of VTE-events at 6 months displayed that 23.4 (95% CI 18.4-29.4) had been classified as high risk at baseline, and the remaining events presented in patients categorized as low- or intermediate risk. Patients with a score of 3 or higher had a 90% (RR 1.9, 95% CI 1.5 - 2.3) increased risk of a VTE compared to patients allocated less than three points.	Present study evaluated the performance of a risk stratification model for VTE in cancer patients, the Khorana risk score, in a meta-analysis with extracted data from 55 published studies. **Limitations** - In meta-analysis, there are major potential for bias due to the heterogeneity in methodology between studies included, however current meta-analysis used - There are potential conflicts of interest, three of the authors reports either having an advisory role or received endorsements (personal or research) from pharmaceutical companies. **Strengths** The systematic search adheres to the PRISMA guidelines for systematic search. A major strength is the meta-analysis design, and the large amount of studies enabling subgroup analysis in different cancer types. Further the study allow The study accounted for between study heterogeneity.	

Reference: Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008;111(10):4902-7.

GRADE	
Quality of evidence	Moderate/low
Recommendations	N/A

Aim	Material and methods	Results	Discussion/Comments
To develop a risk assessment model to assess risk of venous thromboembolism applicable to ambulatory cancer patients receiving chemotherapy **Conclusion** The developed and internally validated risk assessment model for VTE in ambulatory cancer patients receiving chemotherapy can be used to identify short-term high risk for VTE. **Country** USA **Year Data Collection** March 2002-October 2006	**Study design**: Multicentre prospective observational study. **Population**: Patients with a confirmed cancer diagnose. All different cancer sites was eligible, but **Eligibility**: About to initiate chemotherapy and expected to follow at least four cycles. **Exclusion criteria:** Under 18 years of age, concurrent use of cytotoxic, biological or immunological therapy for comorbidities. Acute leukemia diagnoses was excluded **Exposure:** Malignant disease and treatment with chemotherapy **Outcome**: Symptomatic deep vein thrombosis and/or pulmonary embolism during 6 months follow-up. **Statistical methods**: Split sample, two thirds of the population was used in development of the study and one third was used in the internal validation. Multivariate forward stepwise regression model.	**Main results**: In the univariate analysis, parameters that were associated with symptomatic VTE at a significance level set to .05 was identified. A multivariate analysis comprised of the identified parameters was performed. Based on the regression coefficients, a model was developed resulting in a finished RAM: **Variable** — **Score** Very high-risk tumor (stomach, pancreas) — 2 High-risk tumor (lung, gynecologic, genitourinary excluding prostate) — 1 Hemoglobin level <100 g/L or use of red cell growth factors — 1 Prechemotherapy leukocyte count >11 × 10^9/L — 1 Prechemotherapy platelet count 350 × 10^9/L or greater — 1 Body mass index 35 kg/m^2 or greater — 1 A score of 0 = low-risk category. A score of 1–2 = intermediate-risk category. A score of >2 = very high-risk category. Categories based on the model score was: Low risk group (score 0), intermediate risk group (1-2) and high risk group (3 points or more) Internal validation at a cut-off of 3 points or more: - Sensitivity of 40% - Specificity of 89% - Positive predivtive value (PPV) of 7.1% - Negative predictive value (NPV) of 98% - C-statistic of 0.7.	Five parameters were identified as predicative for symptomatic VTE in ambulatory cancer patients receiving a new chemotherapy regimen. Internal validation was performed through a split sample approach. Validation displayed a C-statistic of 0.7. **Limitations** The cohort was originally designed to investigate a different study aim. The VTE-events were not objective adjudicated, but diagnosed by treating physician. **Strengths** The cohort had a large study size (n=4066), with only 3% lost to follow up.

Reference: Rupa-Matysek J, Lembicz M, Rogowska EK, Gil L, Komarnicki M, Batura-Gabryel H. Evaluation of risk factors and assessment models for predicting venous thromboembolism in lung cancer patients. Med Oncol. 2018;35(5):63.			**GRADE** Quality of evidence: Low Recommendations: N/A
Aim	**Material and methods**	**Results**	**Discussion/Comments**
Investigate the prognostic significance of current RAMs for predicting VTE in lung cancer patients in an outpatient setting. **Conclusion** The COMPASS-CAT model was the most accurate predictor for VTE development in lung cancer patients. **Country** Poland **Year Data Collection** January 2016-December 2017	**Study design**: Retrospective case-series **Data foundation**: Newly diagnosed lung cancer patients at an outpatient clinic at the Department of pulmonology, Allergology and pulmonary oncology at Poznan university of Medical Sciences, Poland. **Information collection**: Information was gathered through review of patient files. **Exclusion criteria**: Not specified. **Exposure**: Ambulatory treatment with chemotherapy in lung cancer patients. **Outcome**: Objectively confirmed symptomatic VTE **Statistical methods**: Chi-square test for categorical variables and Mann-Whitney U test was used for continuous variables. Reciever operating characteristics (ROC) curves was calculated to evaluate performance of the RAM..	Of 118 lung cancer patients, 16.9% experienced a VTE in the median 2.5 months. During a median follow-up of 14 months, 64% of patients died. Multivariate analysis displayed high COMPASS-CAT (OR 8.7, 95% CI 1.0-75.2), gemcitabine chemotherapy (OR 3.4, 95% CI 1.1-10.4) and atrial fibrillation (OR 7.2, 95% CI 1.9-27.3) associated with VTE. **Khorana risk score:** The rate of VTE by the Khorana risk score (KRS) was 17% in the intermediate risk group and 13% in the high risk group. Corresponding to a sensitivity of 10%, specificity of 100%, positive predictive value (PPV) of 17% and negative predictive value (NPV) of 83%. **Protecht risk score:** The rate of VTE by the Protecht score was 16% in the low risk group and 17.7% in the high risk group. Corresponding to a sensitivity of 20%, specificity of 78%, PPV of 18% and NPV of 84%. **CONKO risk score:** The rate of VTE by the CONKO score was 17.4% in the high risk group and 15% in the low risk group. Corresponding to a sensitivity of 55%, specificity of 48%, PPV of 15% and NPV of 82%. **COMPASS-CAT score**: The rate of VTE was 0% in the low risk and 23.8% in the high risk group by the COMPASS-CAT. Corresponding to a sensitivity of 100%, specificity of 35%, PPV of 24% and NPV of 100%	Present study found in a relatively homogenous group of lung cancer patients undergoing outpatient chemotherapy that the RAM with best discriminatory ability was COMPASS-CAT. Their findings on the association between venous thrombosis and atrial fibrillation are in line with previous literature. **Strengths**: Comparison of different RAMs on a study sample from a single reference hospital centre. **Limitations:** The study has several limitations. Primarily the retrospective design. However, the baseline measurement are obtained before chemotherapy was initiated as the parameters are routinely checked. The identification of patients and the extraction of parameters are not well specified in the methods. Another limitation is the small sample size, resulting in few events in the stratified groups by the different RAMs. Hence interpretation of the findings should be done with extreme caution.

Reference: Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med. 2006;166(4):458-64.			**GRADE**	
			Quality of evidence	Moderate
			Recommendations	N/A
Aim	**Material and methods**	**Results**	**Discussion/Comments**	
To determine the incidence and time course of the development of VTE using a large cohort of cancer patients. **Conclusion** The incidence of VTE varied with cancer type. The incidence rate of thromboembolism decreased over time. Diagnosis of thromboembolism during the first year of follow-up was a significant predictor of death for most cancer types and stages analyzed. **Country** USA **Year Data Collection** 1993-1997	**Study design**: Prospective observational study **Data foundation**: The California cancer registry was linked to the California patient discharge data set using social security numbers. **Exclusion criteria:** Non-melanoma skin cancers, previous VTE-events before inclution **Exposure:** Cancer diagnosis **Outcome**: Deep vein thrombosis or pulmonary embolism during 2 years of follow-up **Statistical methods**: Cox proportional hazard was used to obtain age-and cancer stage adjusted hazard ratios. Kaplan-Meyer plots were used to display the incident of VTE by different cancer types.	**Main results:** A total of 234 149 cancer patients were identified. The incidence rate of VTE was higher the first year of follow—up, compared to the second for all cancer types. The cancer types with the highest incidence of VTE was advanced pancreatic-, gastric-, bladder-, uterine-, renal- and lung cancer. Metastatic disease at diagnosis was associated with a 20-fold higher risk of VTE compared to localized disease. However, the incidence was substantial in regionalized disease also, displayed in the KM:  In multivariate analysis adjusted for age, stage-and site of cancer, experiencing a VTE within the first year after diagnosis was associated with a decreased survival for all cancer types (HR 1.6—4.2)	Current study explored the absolute and relative risks between cancer and venous thromboembolism in a large cancer cohort. They found that the incidence of experiencing a VTE is greatly increased during the first year following a cancer diagnosis. Incident VTE was significantly associated with a decreased survival sub group analysis of all cancer sites and stages. The authors mention that this might be due to complications of a VTE or subsequent treatment with anticoagulants. **Limitations**: The study did not include for treatment-related factors, as information on chemotherapy, radiation therapy or hormonal anti-cancer treatment was not available. Further, information on whether patients received primary thromboprophylaxis was unknown. **Strengths**: The large sample size with relatively long follow-up increase the generalizability of the findings.	