Thrombosis Research 191S1 (2020) S50–S57

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Overview of risk assessment models for venous thromboembolism in ambulatory patients with cancer

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ARTICLE INFO

Keywords:
Risk assessment model
Venous thromboembolism
Cancer-associated thrombosis
Cancer

ABSTRACT

Important progress has been made in the development of risk assessment models (RAM) for the identification of outpatients on anticancer treatment at risk of venous thromboembolism (VTE). Since the breakthrough publication of the original Khorana risk score (KRS) more than 10 years ago, a new generation of KRS-based scores have been developed, including the Vienna Cancer and Thrombosis Study, PROTECHT, CONKO, ONCOTEV, TicOnco and the CATS/MICA score. Among these the CATS/MICA score showed that a simplified score composed of only two calibrated predictors, the type of cancer and the D-dimer levels, offers a user-friendly tool for the evaluation of cancer-associated thrombosis (CAT) risk. The COMPASS-CAT score is the first that introduced a more synthetic approach of risk evaluation by combining cancer-related predictors with patient comorbidity in a score which is designed for the types of cancer frequently seen in the community (i.e. breast, lung colon or ovarian cancers) and has been externally validated in independent studies. The Throly score is registered as part of the same group as it has a similar structure to the COMPASS-CAT score and is applicable in patients with lymphoma. The incorporation of specific biomarkers of hypercoagulability to the RAM for CAT offers the possibility to perform a precision medicine approach in the prevention of CAT. The improvement of RAM for CAT with artificial intelligence methodologies and deep learning techniques is the challenge in the near future.

Highlights

- A routine assessment to identify patients at high risk of cancer-associated thrombosis (CAT) is recommended by international and national guidelines
- The original Khorana risk score (KRS) and the new generation of KRS-based scores are based on the thrombogenicity of the cancer and offer the possibility to assess risk for CAT in patients with a large spectrum of types of cancer.
- The COMPASS-CAT score is designed for patients with specific types of cancer frequent in the community (breast, lung, colon or ovarian cancer) and combines predictors related to the cancer and to a patient's intrinsic risk factors and comorbidities and has been independently validated. The ThroLy score is specific for lymphoma patients.

1. Introduction

Among cardiovascular disorders, venous thromboembolism (VTE), despite being a preventable disease, still remains a major health problem, especially when it occurs in cancer patients; in this specific case it is described by the term cancer-associated thrombosis (CAT).

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Received 25 September 2019; Received in revised form 15 January 2020; Accepted 23 January 2020
This article was published as part of a supplement sponsored by the International Conference on Thrombosis and Hemostasis Issues in Cancer.

Currently, the average incidence of symptomatic VTE in patients who receive anticancer therapy is about 10%, with approximately 544,000 CAT-related deaths every year in Europe. Thus, CAT figures as a second cause of mortality after cancer itself [1–7]. The risk of VTE increases by about sixfold in outpatients on chemotherapy or with advanced stage of the disease [8–10]. Most importantly, the vast majority of VTE events occur in cancer patients who are not hospitalized. Furthermore, the occurrence of CAT dramatically impacts the survival possibilities. The mortality rate of cancer patients with CAT is two- to threefold higher compared to those without. Furthermore, CAT occurrence leads to modifications of the anticancer treatment schedule, as patients with CAT must receive long-term anticoagulant therapy which exposes them to a significantly higher risk of major bleeding compromising the administration of anticancer treatment [11]. In addition, CAT figures among the leading causes for prolonged hospitalization and rehospitalization, thus causing a substantial increase of expenditure for the health systems [12]. The direct cost of CAT on EU health systems is up to €1.5–2.2 billion each year, mostly derived from hospitalization of patients with CAT [13]. In France, for instance, CAT is the most frequent diagnosis leading to hospital admission in patients with breast or prostate cancer. The average cost per stay for the first thrombotic event is about €3,611 [14].

CAT is an underestimated problem in the community of oncologists despite its major impact on survival, quality of life and macroeconomics of the health insurance systems. A routine assessment to identify patients at high risk for CAT is recommended by international and national guidelines [15–19]. However, according to the European Society of Medical Oncology (ESMO) “most oncologists underestimate the prevalence of CAT and its negative impact on their patients” [20]. According to the most modern concept acknowledged by the recent recommendations published by ASCO experts, oncologists and members of the oncology team should educate patients regarding VTE, particularly in settings that increase risk, such as major surgery, hospitalization, and while receiving systemic antineoplastic therapy [21].

The rate of symptomatic VTE in outpatients on chemotherapy does not justify routine pharmacological thromboprophylaxis. The potential benefit of pharmacological thromboprophylaxis is compromised by the increased bleeding risk associated with this treatment and is enhanced by conditions related to the malignancy and its treatment (i.e. thrombocytopenia, renal insufficiency, liver toxicity, etc.). The high variability of the rate of symptomatic VTE in cancer outpatients on chemotherapy (from 2% to 20%) reveals the high heterogeneity of this group of patients. Risk factors that determine the risk of VTE have been identified from population-based databases, registries, hospital records, retrospective cohorts, prospective observational studies, and clinical trials. Such factors are the type of cancer, the stage of the disease, the time since diagnosis of the cancer or its recurrence, the type of the anticancer therapies and the supportive treatments. In addition, the global risk is influenced by patient-related intrinsic risk factors such as comorbidities (i.e. cardiovascular risk factors, autoimmune diseases related or not with the cancer), personal history of VTE or presence of thrombophilia or genetic polymorphisms related with risk of VTE. In this complex terrain, the identification of patients at risk is a challenging issue. The accurate individual evaluation of VTE risk and the identification of patients eligible for pharmacological thromboprophylaxis is a clinical need. To this aim, risk assessment models (RAM) for individual thrombotic risk evaluation have been developed. In this review, we will present the actual status in the development of risk assessment tools for the prevention of CAT and the perspectives for improving accurate identification of outpatients with cancer on chemotherapy.

2. The Khorana risk score: a breakthrough step in CAT prevention

The first and most widely known RAM for CAT in outpatients with solid tumors was presented by Khorana et al. in 2008 [22]. The Khorana risk score (KRS) was constructed by a post hoc analysis of a database from the Awareness of Neutropenia in Chemotherapy Study Group registry. The predictors of the KRS include the tumor type dichotomized to very high-risk cancers (stomach, pancreas) and high-risk cancers (lung, lymphoma, gynecologic, bladder, testicular, renal). Interestingly, common cancers in the community such as those of the breast, prostate and colon as well as brain tumors and urological cancers are not included in the score. However, according to an alternative interpretation, all cancer patients can be assessed with the KRS. Those with cancers which are not represented in the score get the value “0” for this predictor. The predictors of the score include the body mass index (BMI) as a patient-related factor. Lastly, the KRS includes some hematological markers (prechemotherapy levels of hemoglobin, platelets and white blood cells) which are nonspecific for blood hypercoagulability (Table 1). The original KRS has been derived and validated to evaluate VTE risk in outpatients before the initiation of chemotherapy. The KRS is a weighted scoring system. Patients with a score ≥3 are classified as being at a high risk level. The accuracy of the KRS has been studied in more than 50 studies which are marked by high heterogeneity regarding the types of cancers, the duration of the follow-up, the timing of patient assessments (before or after the initiation of chemotherapy), the type of the anticancer treatment and the definition of the thromboembolic outcomes (reviewed in [23]) Due to this heterogeneity, the accuracy of the KRS is a matter of controversy. Five cohort studies evaluated the Khorana score in patients with a mix of cancer types. Two prospective studies conducted in ambulatory patients with cancer and one prospective study in patients with cancer undergoing insertion of a central venous port showed that patients with a higher score had a higher risk of VTE [24–26]. In the central venous port study, the association between KRS and catheter-related VTE was of borderline significance (odds ratio (OR) 3.50, 95% confidence interval (CI) 1.00–12.30), underlining that the risk of catheter-related thrombosis should not be assessed with the KRS since it is a distinct entity. Patell et al. [27] applied the KRS to hospitalized patients with cancer. This study reported that patients with a high KRS (>3) were significantly more likely to develop VTE during hospitalization than patients with a low KRS (multivariable OR 2.52, 95% CI 1.31–4.86). Similar results were reported in a multicenter retrospective study of 1398 hospitalized patients [28]. In this analysis, inhospital VTE occurred in 5.4% (95% CI 1.9–8.9%) of high-risk patients, 3.2% (95% CI 2.0–4.4%) of intermediate-risk patients, and 1.4% (95% CI 0.3–2.6%) of low-risk patients (OR for high- to low-risk patients 3.9, 95% CI 1.4–11.2). These two studies documented that the risk of VTE should not be neglected in hospitalized cancer patients and can be assessed with the appropriate cancer-specific score. More recent studies showed that the KRS has limited accuracy in the evaluation of VTE risk in patients with lung cancer, pancreatic

Table 1
The Khorana risk assessment model for CAT applicable in out-patients before the initiation of chemotherapy [22]

Patient characteristic	Points
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular, renal)	1
Prechemotherapy platelet count ≥350 G/L	1
Hemoglobin level <100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count >11 g/L	1
Body mass index ≥35 kg/m^2	1
Calculate total score, adding points for each criterion in the model	
Interpretation	
High-risk	≥3
Intermediate-risk	1–2
Low-risk	0

cancer, hepatocellular carcinoma or hematological malignancies [29–34]. A recently published systematic review and meta-analysis, specifically focusing on 6-month follow-up outcomes of all published relevant studies, evaluated the accuracy of the KRS [23]. A total of 45 articles and eight abstracts were included in the analysis, comprising 55 cohorts and 34,555 ambulatory cancer patients, of whom 2,386 (6.9%) were diagnosed with VTE during follow-up. The rate of VTE in patients with high KRS was 11%, being significantly higher than in those with intermediate KRS (6.6%) or low KRS (5.0%). Within the high-risk group, the estimated risk of VTE was considerably lower for patients with lung cancer and hematologic malignancies than for those with other cancer types. Thus, the performance of the KRS varies across tumor types confirming the findings of the isolated studies as mentioned above. Furthermore, the VTE incidence in patients with a low to intermediate KRS was 5–7%, which indicates that the residual risk in this group is still substantial. Therefore, according to the authors, the Khorana score is of limited use in ruling out a future VTE event. Lastly, the KRS is designed to select patients in the high-risk group for thromboprophylaxis. As underlined by the authors, about one in four (23.4%, 95% CI 18.4–29.4%) of the VTE events occurs in patients with a high-risk Khorana score. This means that a substantial amount of cancer patients with subsequent VTE events will not be identified with this form of risk stratification, and will, therefore, not benefit from thromboprophylaxis.

The KRS has been used as a tool for risk stratification in two recently published clinical trials which assessed the efficacy and safety of the direct orally active factor Xa inhibitors rivaroxaban and apixaban to prevent CAT in outpatients receiving chemotherapy. The CASSINI study – a double-blind, randomized trial involving 1,080 high-risk ambulatory patients with cancer (KRS ≥ 2, on a scale from 0 to 6) – randomized patients to receive either rivaroxaban (10 mg o.d.) or placebo for up to 180 days. Interestingly, the cut-off of the KRS in the CASSINI study was set at 2 although the original score had 3 points as the cut-off value. This choice was based on the analysis of the data derived from the Vienna Cancer and Thrombosis Study (Vienna-CATS), which used the KRS to monitor 819 ambulatory patients with cancer for symptomatic VTE. The Kaplan–Meier analysis demonstrated that the cumulative probability of VTE after 6 months was 17.7% (95% CI 11.0–27.8%; $n = 93$) in patients with a Khorana score ≥ 3 and 9.6% (95% CI 6.2–14.7%; $n = 221$) in patients with a Khorana score of 2 [35]. The CASSINI trial failed to demonstrate any significant decrease in the symptomatic VTE rate in the rivaroxaban group (6%) versus the control group (8.8%; hazard ratio (HR) 0.66, 95% CI 0.40–1.09; $p = 0.10$) in the 180-day trial period [36].

The AVERT trial had a similar design to the CASSINI study and compared the efficacy and safety of thromboprophylaxis with apixaban 2.5 mg twice daily ($n = 288$) versus placebo ($n = 275$) in ambulatory patients with cancer who were at intermediate to high risk for VTE. The follow-up period was 180 months. The AVERT trial, similarly to the CASSINI, assessed patients with the KRS and enrolled those at intermediate to high risk level. Eligible patients were those with a score ≥ 2. The AVERT trial showed that thromboprophylaxis with apixaban significantly reduced the rate of VTE (4.2%) as compared to placebo (10.2%; HR 0.41, 95% CI 0.26–0.65; $p < 0.001$) in the 180-day trial period [37]. However, careful analysis of the Kaplan–Maier curves in both trials shows that during the first 2 months after patient enrollment very few, if any, VTE events occurred in the placebo and the intervention group. Taking into consideration that about 80% of VTE occurs within the first 3 months from chemotherapy initiation, these results are surprising.

The design of both trials (CASSINI and AVERT) was similar to that of the SAVEONCO study [38] which compared the efficacy and safety of the ultra-low molecular weight heparin semuloparin versus placebo in outpatients on chemotherapy. In the three studies, the defined intervention period for the primary analysis was 180 days. The main difference in the design was that patients in the CASSINI and the AVERT trial were assessed for VTE risk with the KRS and were eligible if the score was ≥ 2, whereas those enrolled in the SAVEONCO were selected on the basis of an empirical assessment of VTE risk factors (history of VTE, central venous catheter, obesity, aged 75 years or older, chronic respiratory failure, chronic heart failure, venous insufficiency or varicose veins, and use of hormonal therapy). The application of the KRS in the CASSINI and AVERT trials resulted in enrollment of patients at higher thromboembolic risk compared to those enrolled in the SAVEONCO study. This is documented by the two- to threefold higher rates of VTE events observed in the placebo groups of the CASSINI and AVERT trial as compared to the placebo group of the SAVEONCO study (8.8% and 10% versus 3.4%, respectively). The rates of VTE in the intervention groups were 6% in CASSINI, 4.2% in AVERT and 1.2% in SAVEONCO. On the other hand, the rate of major bleedings in the intervention groups were 2% in CASSINI, 3.5% in AVERT and 1.2% in SAVEONCO, whereas the rates of the safety outcomes in the control groups were 1% in CASSINI, 1.8% in AVERT and 2.8% in SAVEONCO. Although a direct comparison between the three antithrombotic agents is not feasible, it seems that the application of a calibrated RAM results in enrollment of patients at higher risk and in an improvement of the benefit to risk ratio of pharmacological thromboprophylaxis.

3. The new generation of KRS

New scores have been developed, namely the Vienna-CATS, PROTECHT, CONKO, ONCOTEV and TicOnco, which share the same structure as the original KRS, and are derived from prospective observational cohort studies. The new generation of the KRS include biomarkers specific for hypercoagulability aiming to improved accuracy in the identification of patients at high risk [35,39,40].

The new generation of KRS is based on the concept that cancer type is the determinant predictor of the risk for VTE. As with the original KRS, cancers are stratified in two groups: 1) very high-risk tumors, which include pancreatic and gastric cancer that score 2 points; and 2) high-risk tumors which include lung, gynecological, lymphoma, bladder or testicular cancer that score 1 point. Common cancers such as breast, colon or prostate cancer are considered as low risk for CAT and score zero points. BMI ≥ 35 kg/m^2 figures among the predictors. The new generation of the KRS are summarized and compared in Table 2. The PROTECHT score introduced the type of chemotherapy and particularly gemcitabine treatment as a predictor. The CONKO score replaced the BMI predictor with a World Health Organization performance status > 2.

As with the original score, the new generation of the KRS includes biomarkers non-specific for blood hypercoagulability, such as prechemotherapy levels of hemoglobin, leucocytes and platelet count which are related with cancer aggressiveness or are usually abnormal in frail cancer patients. The major step forward of the new generation of the KRS is the introduction of the biomarkers of hypercoagulability in the Vienna-CATS score which significantly improved the positive predictive value (PPV) of the score. The sensitivity of the Vienna-CATS RAM at the cut-off point for highest risk (score ≥ 5) at 6 months was 19.1%, the specificity was 98.2%, and the PPV and NPV (NPV) were 42.9% and 94.4%, respectively.

The new generation of the KRS has been externally validated in multinational, prospective cohort study. The performance of the KRS, Vienna-CATS, PROTECHT, and CONKO scores was evaluated in 876 patients with solid cancers at stage III or IV [41]. The c-statistics of the scores ranged from 0.50 to 0.57. 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 KRS to 9.6% (95% CI 6.6–13%) for the PROTECHT score. High-risk patients had a significantly increased risk of VTE when assessed with the Vienna-CATS (sub-hazard ratio 1.7, 95% CI 1.0–3.1) or PROTECHT (sub-

Table 2
Structure of the new generation of risk scores and comparison to the original Khorana risk score

Predictor	Khorana score [22]	Vienna-CATS score [35]	PROTECHT score [39]	CONKO score [40]	ONKOTEV score [43]	TicOnco [44]
Pancreatic or gastric cancer (very high risk tutors)	2	2	2	2	KRS ≥2 = 1	2
Lung, gynecological, lymphoma, bladder or testicular (high risk tutors)	1	1	1	1		1
Prechemotherapy hemoglobin <110 g/L or use of erythropoietin	1	1	1	1		1
Prechemotherapy leucocyte count $>11\times10^9$/L	1	1	1	1		1
Prechemotherapy platelet count >350 G/L	1	1	1	1		1
Body mass index ≥35 kg/m^2	1	1	1	-		1
Previous venous thromboembolism					1	
Metastatic disease					1	
Vascular/lymphatic macroscopic compression (detected by MRI)					1	
World Health Organization performance status >2	–	–	–	1	–	
D-dimer>1.44 μg/L	–	1	–	–		
Soluble P-selectin>53.1 ng/L	–	1	–	–		
Single nucleotide polymorphism	–	–	–	–	–	1
Gemcitabine chemotherapy	–	–	1	–		
Platinum-based chemotherapy	–	–	1	–		

MRI, magnetic resonance imaging.

hazard ratio 2.1, 95% CI 1.2–3.6) score. The external validation cohort enrolled patients with breast cancer (9%), prostate cancer (16%) colorectal cancer (16%) and esophageal cancer (17%). Patients with pancreas or lung cancer represented 35% of the cohort. Moreover only 30% were chemotherapy naive when assessed.

Rupa-Matysek et al. in a retrospective analysis of 118 patients with lung cancer independently evaluated the KRS, the PROTECHT score and the CONKO score in the prediction of CAT [42]. This study confirmed the low accuracy of the KRS in the context of lung cancer and demonstrated that both the PROTECHT and the CONKO score had a low performance to identify patients at high risk of VTE.

The ONKOTEV score [43] and the TicOnco score are the most recent KRS-based risk assessment models for CAT in outpatients with solid tumors who receive chemotherapy. The ONKOTEV has been derived from a prospective study which enrolled 843 patients with solid tumors. The derivation cohort included patients with breast cancer (36.6%), gastroentero-pancreatic cancer (30%) genito-urinary tract cancer (12.9%) and lung cancer (4%). An ONCOTEV score higher than 2 had better performance that the original KRS. However, the ONCOTEV score has not been validated externally.

The TicOnco score derived from a prospective study which enrolled 319 patients with colorectal (51%), oesophago-gastric (22%), lung (27%), or pancreatic cancer (22.5%) [44]. Patients were genotyped for single nucleotide polymorphisms (SNPs) of the genes for F5rs6025, F5rs4524, F2rs1799963, F12rs1801020, F13rs5985, SERPINC1rs121909548, SERPINA10rs2232698 and A1 blood group. The risk of VTE associated with the primary tumor site (low, high, and very high) was categorized as when determining the KRS, and the most clinically relevant SNP were identified by multivariate analysis. The TicOnco score, which is composed of the KRS and the SNP, showed an area under the curve (AUC) of 0.73 (0.67–0.79), a sensitivity of 49%, and a specificity of 81%. Its PPV was 37%, NPV 88%, platelet to lymphocyte ratio was 2.6, and neutrophil to lymphocyte ratio was 0.6%. The KRS showed a significantly lower capacity to identify patients at risk of CAT compared with the TicOnco (AUC 0.73 versus 0.58 respectively; $p<0.001$). The sensitivity of the TicOnco score was significantly higher than that of the Khorana (49% versus 22%; $p<0.001$), while the specificities of both scores were similar (81% versus 82%; $p=0.823$). The PPV and NPV of the TicOnco score were significantly higher than those of the Khorana score (37 versus 22%, $p=0.004$ for PPV; and 88 versus 82%, $p<0.001$ for NPV). Noteworthy, the overall incidence of VTE was 18%. Patients suffering from pancreatic cancer experienced VTE at a significantly higher frequency (40%) than patients with other type of cancers and, probably, pancreatic cancer had a major impact on the accuracy of the TicOnco score. In addition, the TicOnco score has not been externally validated.

More recently, Pabinger et al. reported on the development and validation of a RAM (CATS/MICA score) that utilizes only two variables: type of cancer and a continuous scale of D-dimer levels of the latter for different types of cancers [45]. The development cohort (CATS) included 1,423 patients and the validation cohort (MICA) included 832 patients. Patients enrolled in CATS/MICA study had lung cancer (21%), lymphoma (17%), breast cancer (16%), colorectal cancer (12%), prostate cancer (11%), pancreatic cancer (8%), stomach cancer (4%), kidney cancer (3%) and esophageal cancer (1%). Among a large number of clinical parameters and biomarkers of hypercoagulability the multivariate analysis identified the tumor site risk category (very high versus high and high versus low or intermediate) and continuous D-dimer concentrations as major predictors for VTE. In this model, the multivariable sub-distribution HRs were 1.96 (95% CI 1.41–2.72; $p=0.0001$) for very high versus high and high versus low or intermediate risk categories and 1.32 (1.12–1.56; $p=0.001$) per doubling of D-dimer concentration. The cross-validated c-index of this model was 0.66 (95% CI 0.63–0.67). The model has been simplified in a user-friendly nomogram. With the cut-off for predicted cumulative 6-month risk of venous thromboembolism in CATS set at 10%, the sensitivity of the model was 33%, the specificity was 84%, the PPV was 12%, and the NPV was 95%. At a cut-off of 15%, the sensitivity of the model was 15%, the specificity was 96%, the PPV was 18%, and the NPV was 95%. Further data are expected about the ability of this new tool to predict the effect of thromboprophylaxis.

4. The third generation of RAM for CAT

Data from fundamental, epidemiological and clinical research on CAT led our group to introduce a method for VTE risk evaluation which is based on two principles: 1) focus on frequent types of cancer in the community (i.e. breast, lung, colon, and ovarian cancer) or specific hematological malignancies (i.e. lymphoma); and 2) combines cancer-related risk factors with patient-related intrinsic risk factors. Cancer-related risk factors include the type of cancer, time since cancer diagnosis, types of anticancer treatments and associated devices, and stage of the cancer. Patient's intrinsic risk factors included cardiovascular risk predictors, personal history of VTE and recent (less than 3 months) hospitalization for acute medical illness. Each predictor

has been weighted and calibrated at the derivation cohort and has different impacts in the global score.

Since thrombogenic potential varies according to the type of cancer, we promoted studies enrolling patients with specific types of cancer. This concept led to the COMPASS-CAT (clinical studies) and ROADMAP-CAT (hypercoagulability biomarkers studies) [46–48] program which aimed to derive clinico-biological risk assessment models specific for types of tumors. The ROADMAP project, developed in parallel with the HYPERCAN [49,50] and Vienna-CAT [25,51,52], show that biomarkers of hypercoagulability such as thrombin generation test, procoagulant phospholipid clotting time, D-dimers, von Willebrand factor levels and P-selectin have some clinical pertinence and may improve the PPV of the clinical RAMs.

5. The COMPASS-CAT score

The multicenter, prospective, observational COMPASS-CAT study was undertaken in 1,355 outpatients with breast, colon, lung or ovarian cancer [53]. These types of cancers are common in the community and are related to a high absolute burden of VTE episodes. Most of the patients (89%) were on anticancer treatment when enrolled in the study. Half of them were on anticancer treatment for a median of 3 months. The multivariate analysis led to the derivation of the COMPASS-CAT score (Table 3). The score at the cut-off value for high risk level (≥ 7) had an NPV of 98% and a PPV of 13%. The sensitivity and the specificity of the COMPASS-CAT RAM was 88% and 52%, respectively. The receiver operating characteristic analysis showed an AUC of 0.85, indicating very good discrimination capacity of the score.

Rupa-Matysek et al. published the first external validation of the COMPASS-CAT score in patients with lung cancer and compared it with the original and the new generation of the KRS [42]. This study showed that, in patients with lung cancer, the COMPASS-CAT model was a more accurate predictor of VTE risk than the KRS, PROTHEC and KONKO score. Moreover, a cut-off value for high risk level of 11 appeared to improve the accuracy of the score.

More recently, the COMPASS-CAT score was externally validated by Anand et al. [54]. This external validation was a retrospective analysis of a cohort of 3,814 patients, of whom 49%, 5%, 29%, and 17% had breast, ovarian, lung and colorectal cancer, respectively. Symptomatic VTE at 6-month follow-up occurred in 5.85% of patients. The AUC was 0.62. Using model cut-offs of 0–6 or ≥ 7 points, patients stratified into low/intermediate- and high-risk groups had VTE rates of 2.27% and 6.31%, respectively. The sensitivity, specificity, NPV, and PPV of the RAM were 95%,12%, 97.73% and 6.31%, respectively. This large-scale external validation study confirmed the accuracy of the COMPASS-CAT score in outpatients with breast, ovarian, lung and colorectal cancer who receive chemotherapy.

An independent prospective study on patients with lung adenocarcinoma having a similar design as the COMPASS-CAT study evaluated the predictive value of a large panel of biomarkers of hypercoagulability to identify patients at risk of VTE. The ROADMAP-CAT study showed that, in patients with adenocarcinoma of the lung, assessment of thrombin generation with the Calibrated Automated Assay using 5 pM tissue factor and 4 μM procoagulant phospholipids together with the measurement of the procoagulant phospholipid clotting time (Procoag-PPL®) identifies patients at high risk of VTE [45,48]. More importantly, the measurement of these biomarkers before or within 1 month after administration of the first cycle of chemotherapy and their incorporation into the COMPASS-CAT RAM significantly improved the PPV of the score to stratify patients into high or intermediate/low VTE risk groups.

6. The THROLY score

In a prospective multicenter observational study, Antic et al. enrolled 1,820 lymphoma patients with advanced-stage disease who had received at least one chemotherapy cycle split into a derivation cohort (n = 1,236) and a validation cohort (n = 584). Patients had high-grade lymphoma (42.7%), low-grade lymphoma (19.3%), Hodgkin lymphoma (14.6%), chronic lymphocytic leukemia/small lymphocytic lymphoma (14.8%) or other forms of lymphoma (8.6%), and the incidence of symptomatic VTE in the derivation cohort was 5.3% and in the validation cohort was 5.8% [49,55]. Independent predictors of VTE risk were previous venous and/or arterial events, mediastinal involvement, BMI $>30 kg/m^2$, reduced mobility, extranodal localization, development of neutropenia, and hemoglobin level <100 g/L. These predictors composed the Thrombosis Lymphoma (ThroLy) score. The ThroLy score, similar to the COMPASS-CAT score, is specific for lymphoma, is composed of predictors related witoth the malignancy and the patients' intrinsic risk factors for VTE and it is applicable in outpatients after chemotherapy initiation (Table 4). The model produced an NPV of 98.5% (95% CI 97.5–99.1%), and a PPV of 25.1% (95% CI 19.2–31.8%). The sensitivity was 75.4% (95% CI 63.1–85.2%), and the specificity was 87.5% (95% CI 85.5–89.4%). In the validation cohort, the NPV was 97.6% (95% CI 95.9–98.8%), the PPV was 28.9% (95% CI 19.1–0.5%), the sensitivity was 64.7% (95% CI 46.5–80.2%), and the specificity was 90.2% (95% CI 87.4–92.5%). The ThroLy score has been shown to be more precise for lymphoma patients than any other currently available score assessing the risk of thrombosis in patients with malignancy. Compared to the Khorana score, which was able to identify a small (7%) short-term risk of symptomatic VTE in the high-risk group of patients with a sensitivity of 40%, the ThroLy score had a PPV of 25.1%, sensitivity of 75.4%, and PPV for high-risk patients of 65.2%. The external validation of the ThroLy score showed high NPV (97%), although the PPV was 15% [56].

Table 3
The COMPASS-CAT score for VTE risk in patients with breast, lung, ovarian or colon cancer [53]

Predictors for VTE	Score
Cancer-related risk factors	
Antihormonal therapy for women with hormone receptor-positive breast cancer or on anthracycline treatment	6
Time since cancer diagnosis ≤ 6 months	4
CVC	3
Advanced stage of cancer	2
Patient-related predisposing risk factors	
Cardiovascular risk factors (composed by at least 2 of the following predictors: personal history of peripheral artery disease, ischemic stroke, coronary artery disease, hypertension, hyperlipidemia, diabetes, obesity)	5
Recent hospitalization for acute medical illness	5
Personal history of VTE	1
Biomarkers	
Platelets count $\geq 350 \times 10^9$/L	2

Score ≥ 7 designates high risk for VTE and score <7 designates low/intermediate risk of venous thromboembolism (VTE). CVC, central venous catheter.

7. VTE risk assessment in patients with brain tumors

Currently, risk stratification for VTE in patients with primary brain tumors still remains challenging. VTE is a common complication in patients with primary brain tumors, with up to 20% of patients per year having a VTE event [57]. It is noteworthy that brain tumors are missing from all scores that have been developed although, until recently, a risk assessment procedure for VTE in patients with brain tumors was not available. Clinical risk factors for VTE such as glioblastoma subtype, paresis, or surgery are commonly used for this purpose. However, the discriminating capacity of these predictors has not been systematically evaluated. This is a significant drawback since

Table 4
The ThroLy score specific for VTE risk in patients with lymphoma [55]

ThroLy predictors	Score
Advanced stage	2
Previous VTE	2
Reduced mobility	1
Previous AMI/stroke	2
Obesity (BMI > 25 kg/m^2)	2
Extranodal	1
Mediastinum	2
Vascular device	1
Neutropenia	1
Hemoglobin < 100 g/L	1

AMI, acute myocardial infarction; BMI, body mass index; VTE, venous thromboembolism

application of pharmacological thromboprophylaxis in patients with brain tumors is compromised by the bleeding risk and particularly by the risk of intracranial hemorrhage [58]. Specific factors playing a role in tumor biology were recently identified to predispose to prothrombotic risk. Among these are the mutations in the isocitrate dehydrogenase 1 (*IDH1*) gene which occurs in a subgroup of glioma tumors, which correlate with the risk of VTE. Indeed, the incidence of VTE is low in patients with the presence of an *IDH1* mutation compared with those with *IDH1* wild-type status. Expression of the glycoprotein podoplanin on brain tumors was associated with both intratumoral thrombi and high risk of VTE. Podoplanin is a transmembrane glycoprotein with the ability to induce platelet activation via the platelet-receptor CLEC-2. Moreover, podoplanin is a lymphatic endothelial marker and exhibits substantial functions during embryonic development [59]. It is variously upregulated by many cancers including primary brain tumors and linked to inflammation, malignant progression and poor survival [60]. Podoplanin is associated with VTE risk in brain tumor patients, and it could be a useful biomarker to identify patients at very high VTE risk [61]. The clinical relevance of podoplanin and *IDH1* gene status in the evaluation of VTE risk in patients with brain tumors was performed within the framework of the prospective observational cohort of the CATS. The observation cohort enrolled 213 patients with newly diagnosed cancer or with progressive disease after cancer remission. Patients were followed for a period of 2 years. Patients with podoplanin-positive tumors (IHC score +, ++ and +++; n = 151, 71%) were older, had a higher probability of having glioblastoma, and had lower platelet counts and higher D-dimer. A strong inverse association was seen between podoplanin expression levels and *IDH1* mutation, with 55% of the 62 podoplanin-negative tumors, but only 5% of the 151 podoplanin-positive tumors, having an *IDH1* mutation. During follow-up time, VTE occurred in 14% of brain tumor patients. The cumulative 6-, 12- and 24-month VTE risks were 13.0%, 15.4% and 17.0% in patients with *IDH1* wild-type tumors and 0%, 2.4% and 2.4% in patients with *IDH1* mutant tumors, respectively ($p = 0.008$). More interestingly, combined presence of wild-type *IDH1* and high podoplanin expression was associated with increased risk of VTE compared to those with mutant *IDH1* and no podoplanin expression (HR 13.28, 95% CI 1.65–106.97; $p = 0.015$). Measurement of *IDH1* mutation and podoplanin allows differentiation between subgroups of brain tumors that show distinct VTE risk profiles [62]. The incorporation of *IDH1* genotoype and podoplanin levels into a RAM for CAT in patients with brain tumors and its impact on the PPV of the clinical score has to be rapidly evaluated.

8. Discussion

During the last decade, important progress has been made in the development of risk assessment models for the identification of outpatients receiving anticancer treatment at risk of VTE. Following the breakthrough publication of the Khorana risk score for CAT, we possess today a wide panel of risk assessment tools: the original KRS, the Vienna-CATS, PROTECHT, CONKO, ONCOTEV and TicOnco and the CATS/MICA score. These scores have been structured on the concept that the type of cancer is a determinant for the risk of VTE in outpatients who are planned for chemotherapy. Derivation studies showed that the incorporation of biomarkers like D-dimers or genetic SNP increase the accuracy of the KRS. Most importantly, the CATS/MICA score showed that the calibrated association of only two predictors, i.e. the type of cancer and the continuum of the D-dimer values, could provide an easy-to-use tool for rapid evaluation of the thrombotic risk in cancer outpatients. The simplicity of the predictors is the major advantage of KRS and the new generation scores. However, this improvement remains to be confirmed in independent validation studies. Nevertheless, the external validation studies published so far showed that the accuracy of the KRS to identify high-risk patients varies according to the type of cancer. The variability of the anticancer treatment and the variability related with the timing of chemotherapy initiation are parameters that potentially influence the accuracy of these scores.

The COMPASS-CAT RAM and the ThroLy score are the first representatives of a new strategy for the evaluation of VTE in outpatients on chemotherapy that combine cancer-related predictors and risk factors related with patients' comorbidities. The successful external validation of the COMPASS-CAT score in a large retrospective study which included patients with breast, lung, colon or ovarian cancer confirmed the applicability of the new score in real-life outpatients with cancer even if they are on anticancer treatment. The successful independent validation of the COMPASS-CAT score in cohorts of patients with one specific type of cancer (i.e. lung cancer) and that of the ThroLy in patients with lymphoma confirms that the strategy for the derivation of RAM in homogenous cohorts regarding the levels of thrombogenicity of the cancer type is feasible and beneficial for the identification of patients at risk of VTE during the patients' journey with the malignant disease. However, this strategy will lead to the development of many different RAMs and will generate several logistic issues, particularly when these scores will be incorporated into clinical practice. The incorporation of specific biomarkers of hypercoagulability to the COMPASS-CAT RAM offers the possibility to perform a precision medicine approach in the choice of the most appropriate patient for pharmacological thromboprophylaxis.

Today, available RAM offers the clinician the choice of the optimal tool for identification of outpatients at risk of VTE. Taking into consideration that the awareness for the risk of VTE among oncologists is low and the variability of heterogeneity of the group of outpatients with cancer is high, the use of the available validated RAM – independently of the variations of their accuracy – will help to identify high-risk patients eligible for thromboprophylaxis. The recent recommendations of the ASCO encourage the elaboration of multiple additional cohort studies evaluating validation of techniques to further refine current risk stratification approaches or to develop new models that incorporate genetic factors or coagulation-specific biomarkers. Results of these studies could alter our approach to risk stratification in the future. The improvement of RAM for CAT with artificial intelligence methodologies and deep learning techniques is the challenge in the near future.

Conflict of interest statement

The authors do not have any conflict of interest to declare.

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