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Symptom Management and Supportive Care

A Predictive Score for Thrombosis Associated with Breast, Colorectal, Lung, or Ovarian Cancer: The Prospective COMPASS–Cancer-Associated Thrombosis Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Risk assessment model • Cancer-associated thrombosis • Breast cancer • Lung cancer • Ovarian cancer • Colon cancer

Abstract

Background. The stratification of outpatients on chemotherapy for breast, colorectal, lung, and ovarian cancers at risk of venous thromboembolism (VTE) remains an unmet clinical need. The derivation of a risk assessment model (RAM) for VTE in these patients was the aim of the study "Prospective Comparison of Methods for thromboembolic risk assessment with clinical Perceptions and AwareneSS in real life patients–Cancer Associated Thrombosis" (COMPASS–CAT).

Patients and Methods. The derivation cohort consisted of 1,023 outpatients. Patients on low molecular weight heparin (LMWH) thromboprophylaxis were excluded. Documented symptomatic VTE was the endpoint of the study.

Results. Patients had breast (61%), colorectal (17%), lung (13%), or ovarian cancer (8.6%) at localized (30%) or advanced stage (70%). In 64% of patients, cancer was diagnosed within the last 6 months prior to inclusion. Most of them were on chemotherapy when assessed. Symptomatic VTE occurred in 8.5% of patients. The COMPASS–CAT RAM includes the following variables: (a) anthracycline or anti-hormonal therapy, (b) time since cancer diagnosis, (c) central venous catheter, (d) stage of cancer, (e) presence of cardiovascular risk factors, (f) recent hospitalization for acute medical illness, (g) personal history of VTE, and (h) platelet count. At 6 months, patients stratified at low/intermediate and high-risk groups had VTE rates of 1.7% and 13.3%, respectively. The area under the curve of receiver operating characteristics analysis was 0.85. The sensitivity and specificity of the RAM were 88% and 52%, respectively. The negative and positive predictive values of the RAM were 98% and 13%, respectively.

Conclusion. The COMPASS–CAT RAM includes reliable and easily collected VTE risk predictors and, in contrast to the Khorana score, it is applicable after the initiation of anticancer treatment in patients with common solid tumors. Its robustness for stratification of patients at high and low/intermediate VTE risk needs to be externally validated. ***The Oncologist*** 2017;22:1222–1231

Implications for Practice: The Prospective Comparison of Methods for thromboembolic risk assessment with clinical Perceptions and AwareneSS in real life patients–Cancer Associated Thrombosis (COMPASS–CAT) study provides a new risk assessment model (RAM) for venous thromboembolism (VTE) applicable in outpatients with breast, colorectal, lung or ovarian cancer. The COMPASS–CAT RAM is robust, applicable during chemotherapy and determines the need for VTE prévention by including reliable and easily collected VTE predictors associated with cancer status, its treatment as well as with patients' characteristics and comorbidities. An independent external validation of the RAM is indicated before its use in clinical practice.

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Introduction

Venous thromboembolism (VTE) significantly increases the mortality and deteriorates the quality of life for cancer patients [1–3]. The overall incidence of symptomatic VTE in ambulatory patients with breast, colon, lung, or ovarian cancer is approximately 3% [4–7]. However, the risk of VTE increases by sixfold in outpatients on chemotherapy and in patients with advanced disease [8–10]. A risk of this magnitude, as well as the heterogeneity of ambulatory cancer patients, does not justify universal administration of thromboprophylaxis [11]. Thus, a routine assessment to identify patients at high risk for VTE is recommended [12–16]. However, to date, a reliable risk assessment tool for ambulatory patients on anticancer treatment for common solid tumors remains an unmet medical need.

The only currently available risk assessment model (RAM), presented by Khorana et al., was constructed by a post hoc analysis of a database from the "Awareness of Neutropenia in Chemotherapy Study Group" Registry [17]. The Khorana score is applicable in patients with solid tumors at the initiation of chemotherapy and among clinical predictors includes pre-chemotherapy levels of hemoglobin, platelets, and white blood cells count [17–19]. The accuracy of the Khorana score is low when applied to patients with lung, colon, or ovarian cancer. For example, this score was unable to predict cancer-associated thrombosis (CAT) in approximately 70% of a cohort of 3,212 patients enrolled in the SAVE-ONCO study, which assessed the efficacy and safety of semuloparin in primary prophylaxis of VTE [20, 21]. Furthermore, a recent study showed that the Khorana score was unable to predict VTE risk in patients with lung cancer [22]. Therefore, an accurate risk assessment tool applicable for outpatients with breast, colorectal, lung, or ovarian cancer remains an unmet medical need. Taking into consideration that the awareness for VTE prevention among oncologists is not yet optimal, the availability of a RAM applicable to ambulatory patients on anticancer treatment could have an additional educational value by increasing the attention among clinicians about the prevention of CAT.

The multicenter, prospective, longitudinal, non-interventional COMPASS–CAT study (Prospective Comparison of Methods for thromboembolic risk assessment with clinical Perceptions and AwareneSS in real life patients-Cancer Associated Thrombosis) was undertaken in outpatients suffering from breast, colon, lung, or ovarian cancer. The aim of the study was to identify the most relevant risk factors for symptomatic VTE and to develop a RAM applicable to patients after the initiation of anticancer treatment. We here describe the derivation of the COMPASS–CAT RAM.

Materials and Methods

Study Design and Participants

The study was an investigator-initiated multinational, prospective, and non-interventional trial. Ambulatory cancer patients, with histologically confirmed cancer of the breast, lung, colon, or ovaries, were recruited and followed from November 2013 to November 2015. Patients at assessment for inclusion in the study were receiving or were planned to receive the recommended anticancer treatments according to the institutional practices. The exclusion criteria were as follows: (a) age younger than 18 years, (b) life expectancy less than 3 months, (c) ongoing pregnancy, (d) major psychiatric disorders, (e) recent ($<$6 months) episode of VTE or acute coronary syndrome, (f) active anticoagulant treatment (for any indication), (g) scheduled open elective curative surgery under general anesthesia for abdominal, pelvic, or lung cancer, and (h) hospitalization due to stroke, acute coronary syndrome, congestive heart failure, or acute respiratory failure. Consecutive patients from the ambulatory anticancer clinics were assessed for eligibility. At the follow-up visits, at 3, 6, and 12 months after inclusion, patients were interviewed and clinical records were analyzed regarding the occurrence of symptomatic VTE, bleeding episodes, disease evolution, and anticancer treatments. After inclusion in the study, investigators were free to decide whether to apply thromboprophylaxis according to local clinical practice and individual perception of the risk. As per protocol, patients who received any kind of thromboprophylaxis after inclusion were not included in the derivation cohort for the RAM.

All patients enrolled in the study provided written informed consent. The study protocol was approved by the institutional review boards or ethics committees of all participating institutions.

Outcomes

The primary endpoint was symptomatic and objectively confirmed VTE including deep vein thrombosis (DVT), pulmonary embolism (PE), or both (DVT and PE); central venous catheter (CVC) thrombosis or upper limb vein thrombosis (not related to the CVC); or vein thrombosis of rare localization (i.e., splanchnic vein or cerebral vein thrombosis). Symptomatic VTE had to be documented by at least one of the following methods: color Echo-Doppler, computerized tomography, magnetic resonance imaging, angiography, or scintigraphy. The investigators confirmed the occurrence of VTE by analysis of the patients' medical files, taking into consideration the results of the imaging methods and the administration of therapeutic doses of anticoagulant by the treating physician. Patients with incidental VTE were not included in the analysis for the RAM derivation because research for this form of thrombosis has not reached definitive conclusions regarding the need to treat with anticoagulant therapy. Occurrence of VTE and evolution of the disease were registered during the follow-up visits and cross-checked by analysis of the medical records.

Definitions for Key Predictors for VTE

Eligible patients were interviewed at the inclusion visit using a standardized clinical research form (CRF) that included VTE risk factors described in the literature [23–25]. The CRF also assessed the status of the disease, the ongoing treatments, the devices, and the values of hemogram and laboratory parameters of liver and renal function measured within 1 week prior to enrollment. The comorbidities and VTE risk factors non-related to the cancer were defined as follows: renal function was considered as normal if the estimated creatinine clearance rate using Cockcroft-Gault formula was $\geq$60 mL/min per 1.73 m^2. Liver impairment was defined as transaminase increase twofold higher than the upper normal level. The body mass index (BMI) at the day of the assessment was stratified into three groups: normal weight (BMI less than 25), overweight (BMI greater than or equal to 25 and less than 30), or obese (BMI greater than or equal to 30).

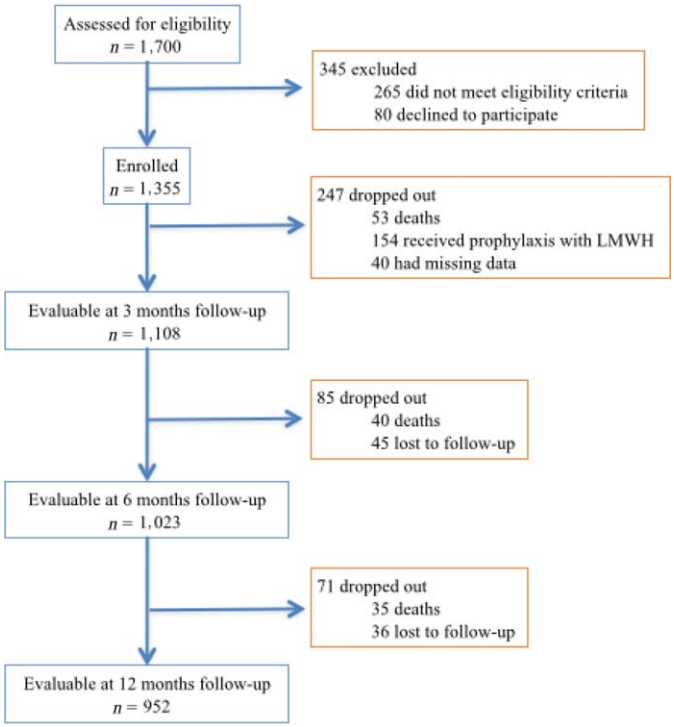


Figure 1. Flow chart of the patients enrolled in COMPASS–CAT study.
Abbreviations: COMPASS–CAT RAM, COMPASS–CAT risk assessment model; LMWH, low molecular weight heparin.

The predictors "hyperlipidemia," "hypertension," "diabetes," "personal history of acute coronary syndrome," "stroke," and "peripheral artery disease" appeared individually in the CRF, were assessed at the inclusion, and refer to objectively diagnosed conditions according to the respective diagnostic criteria. Separate variables were created according to the number of risk factors coexisting in a patient (one, two, three, or four risk factors together) and their relative risk for CAT was evaluated in the multivariate analysis.

Total bed rest with bathroom privileges for >3 days was evaluated if occurring within one month prior to inclusion in the study.

Pulmonary disease includes any active pulmonary disease (except cancer) requiring treatment and present to the patient at least one month prior to inclusion in the study.

The "hospitalization" was defined as hospitalization for any non-surgical reason occurring within the last 3 months before assessment.

The "stage" of cancer was dichotomized into two categories: "local stage" and "advanced stage." The latter was composed of "locally advanced and metastatic disease."

The "time since cancer diagnosis" refers to the time between the day of the assessment and the objective first diagnosis of the cancer or the recurrence of the cancer (if the patient was in complete remission).

The "anti-hormonal therapy" refers exclusively to the treatments recommended for women with hormone receptor-positive breast cancer.

Statistical Analysis

The number of patients included in the study was calculated according to the following assumptions: (a) the model had to be constructed according to the rule of thumb, the so-called events per variable (EPV) 1–10, (b) less than 10 variables should be included in the model in order for it to be easy to use, and (c) it should include the most clinically relevant risk factors for VTE [26–28]. According to the above conditions, the number of independent VTE risk factors that were expected to provide sufficient accuracy of the model was about 5–10 VTE events per risk factor [28]. Thus 50–100 symptomatic VTE events were required to respond to the above conditions. In addition, the total number of patients included in the study was based on the estimation that the mortality during the first 6 months from inclusion would be about 10% and that the fraction of patients lost during follow-up or patients with missing data would be approximately 15%. Continuous variables are described by mean and standard deviation and categorical variables by frequency and percentage. Descriptive statistics for relevant baseline characteristics are provided with corresponding frequency and standard deviation or interquartile range (depending on a Gaussian or a skewed distribution). The chi-square test was used to identify baseline differences in qualitative variables between patients who presented symptomatic VTE and patients who did not. A comparison of quantitative variables between two groups was performed using the Student's *t* test, depending on the distribution of the data. Patients who, after the inclusion, received pharmacological thromboprophylaxis were excluded. Patients who had no missing data at 6 months from inclusion were used for the derivation of the model.

The model development started by defining the symptomatic documented index VTE event as the dependent variable. The first step consisted of the univariate analysis to identify the variables associated with VTE risk. The selection of independent variables was done at the level of 5% using the stepwise procedure.

Table 1. Demographic data, cancer characteristics and associated treatments, comorbidities, and risk factors for VTE non-related to the cancer in the derivation cohort of evaluable patients at 6 months follow-up ($n = 1,023$)

Characteristics	Derivation cohort ($n = 1,023$), *n* (%)
Age (years)	
Mean ± sd	55 ± 12
Range	23–89
Gender	
Male	191 (18.7)
Female	832 (81.3)
BMI	
Normal	427 (41.7)
Overweight	339 (33.1)
Obesity	258 (25.2)
Type of cancer	
Breast cancer	629 (61.5)
Colon cancer	170 (16.6)
Lung cancer	136 (13.3)
Ovarian cancer	88 (8.6)
Stage of cancer	
Localized	307 (30.0)
Locally advanced	311 (30.4)
Metastatic	405 (39.6)
Time since cancer diagnosis	
0–3 months	444 (43.4)
4–6 months	209 (20.4)
7–12 months	101 (9.9)
13–24 months	122 (11.9)
Relapsed cancer	147 (14.4)
Anticancer treatment and devices	
On active treatment when assessed	911 (89.1)
Presence of CVC	326 (31.9)
Type of anticancer treatments	
Anthracycline containing	356 (34.8)
Anti-hormonal therapy	265 (25.9)
Platinum containing	261 (25.5)
Antiangiogenic	197 (19.3)
Radiotherapy	335 (32.7)
Performance status, ECOG	
I or II	920 (90)
III or IV	103 (10)
Comorbidities and VTE risk factors non-related with the cancer	
Hypertension	280 (27.4)
Hyperlipidemia	229 (22.4)
Diabetes	123 (12.0)
Infection	68 (6.6)
Total bed rest with bathroom privileges for >3 days	62 (6.1)
Coronary artery disease	52 (5.1)
Pulmonary disease	49 (4.8)
Chronic obstructive pulmonary disease	49 (4.8)
Liver impairment	34 (3.3)
Renal impairment	26 (2.5)
Peripheral artery disease	25 (2.4)
Ischemic Stroke	15 (1.5)
Heart failure NYHA class I or II	12 (1.13)
Heart failure NYHA class III or IV	2 (0.15)
Varicose veins	137 (13.4)
Hospitalization during the last 3 months prior inclusion	83 (8.1)
Personal history of VTE	59 (5.8)

Abbreviations: BMI, body mass index; CVC, central venous catheter; ECOG, Eastern Cooperative Oncology Group; NYHA, New York Heart Association; VTE, venous thromboembolism.

The multivariable logistic regression model was used to explore the effect of independent variables on VTE risk. The variables found to be significant in the univariate analysis ($p < .05$) and the variables known to be relevant risk factors for VTE (i.e., personal history of VTE) were included in the multivariate analysis. In each step of multivariate analysis, the variable with the highest *p* value was excluded from the model. To prevent erroneous inclusion of predictors into the model, the rule of thumb, EPV 1–10, was applied: one candidate predictor per 10 outcome events was included in the data set [28, 29]. Calibration of the model was controlled with the Hosmer-Lemeshow test. To further evaluate the calibration of the model, patients with VTE were stratified into 10 groups and the number of expected VTE events in each group was plotted against those with observed VTE events. Similarly, the observed number of patients without VTE was plotted against the expected patients without any VTE. The discrimination capacity of the model was tested with receiver operating characteristics (ROC) analysis and the area under the curve (AUC) was calculated. An additional criterion for the selection of predictors included in the model was based on the individual ability to improve the AUC of the ROC analysis. Model discrimination performance was evaluated by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for both cohorts.

Results

Study Population

Derivation Cohort

A total of 1,355 patients were enrolled in the COMPASS–CAT study. Four hundred eighty-nine patients were recruited in Paris (36%), 348 patients in Beyrouth (26%), 214 patients in Amman (16%), 200 patients in Djeddha (15%), 54 patients in Kuwait (4%), and 50 patients in Damas (4%). Among the 1,355 patients, 154 patients (11%) received thromboprophylaxis with the low molecular weight heparin enoxaparin (4,000 anti-Xa IU s.c. daily) for a period ranging from 7–90 days after inclusion.

Table 2. Localization and distribution of VTE according to the type of cancer. Values are number of events and percentage of VTE per type of cancer

Localization of VTE	Breast cancer ($n = 629$), *n* (%)	Colorectal cancer ($n = 170$), *n* (%)	Lung cancer ($n = 136$), *n* (%)	Ovarian cancer ($n = 88$), *n* (%)	Total cohort ($n = 1,023$), *n* (%)
PE	6 (0.95%)	5 (2.94%)	2 (1.47%)	4 (4.55%)	17 (1.66%)
Iliofemoral DVT	4 (0.64%)	1 (0.59%)	2 (1.47%)	1 (1.14%)	8 (0.78%)
Distal DVT	33 (5.25%)	1 (0,59%)	1 (0.74%)	0	35 (3.4%)
ULVT	4 (0.64%)	6 (3.53%)	0	0	10 (0.98%)
CVC thrombosis	7 (1.11%)	3 (1.76%)	0	1 (1.14%)	11 (1,08%)
Other	4 (0.64%)	2 (1.18%)	0	1 (1.14%)	7 (0,68%)
Total	58 (9.22%)	18 (10.59%)	5 (3.68%)	7 (7.95%)	88 (8.6%)

Abbreviations: CVC, central venous catheter; DVT, deep vein thrombosis; PE, pulmonary embolism; ULVT, upper limb vein thrombosis; VTE, venous thromboembolism.

Table 3. Relative risk and 95% confidence intervals of variables, which according to the multivariate regression were significantly associated with the risk of VTE

Predictors of VTE	Relative risk 95% confidence interval, *n* (range)	*p* value
Anthracycline-containing chemotherapy	2.33 (1.02–5.33)	.04
Anti-hormonal therapy in women with breast cancer	6.40 (3.16–12.96)	.0001
Hospitalization	5.41 (2.90–10.08)	.0001
Cardiovascular risk factors and comorbidities (composed by at least two of the following predictors: personal history of peripheral artery disease, ischemic stroke, coronary artery disease, hypertension, hyperlipidemia, diabetes, obesity)	5.18 (1.10–13.40)	.0007
Time since cancer diagnosis ≤ 6 months	4.10 (2.10–7.98)	.0001
CVC	3.24 (1.56–6.72)	.0015
Platelets count $\geq 350 \times 10^9$/L	2.53 1.35–4.74	.0038
Advanced stage of cancer	1.93 (0.92–2.64)	.0048

Abbreviations: CVC, central venous catheter; VTE, venous thromboembolism.

At the end of the follow-up period, 40 patients (3%) were eliminated because of missing data, mainly from the variables of the hemogram, 81 patients (6%) were lost during follow-up because they moved to another location, and 128 patients died. Most of the patients (89.1%) were on anticancer treatment when enrolled. In 43.4% of the patients, cancer was diagnosed within 3 months prior to the enrollment and they were on anticancer treatment for a median of 33 days (minimum 11 days, maximum 90 days; 95% confidence interval [CI], 39–43). In 20% of patients, cancer was diagnosed within 4–6 months before the inclusion into the study and they were on active anticancer treatment for a median period of 98 days (minimum 91 days, maximum 160 days; 95% CI, 109–114). The one-year mortality rate was 9.4%. The flow chart of the patients enrolled in the study is depicted in Figure 1. All centers had comparable rates of mortality, missing data, and lost patients. The demographic and clinical characteristics of the enrolled patients are summarized in Table 1.

Follow-Up and VTE

At 3-months follow-up, 68 patients presented with a symptomatic VTE. At 6-months follow-up, 10 additional patients had symptomatic VTE. At 12-months follow-up, 10 new patients developed VTE, raising the annual incidence of VTE to 8.6%. Analytical data on VTE localization and distribution according to the type of cancer are shown in Table 2. In the subgroup of patients who received thromboprophylaxis with enoxaparin after enrollment in the study, two patients manifested VTE (1.3%) during the 6-months follow-up.

Risk Factors for VTE

In the univariate analysis, the following predictors were found to be significantly associated with the occurrence of symptomatic VTE: overweight or obesity (odds ratio [OR] = 1.80 vs. normal weight; 95% CI, 0.98–2.55; $p = .04$) and hospitalization within 3 months prior to assessment (OR = 3.64, 95% CI, 1.62–6.82; $p < .001$).

The presence of at least one cardiovascular risk factor was associated with a significant increase in the risk of VTE (OR = 3.02, 95% CI, 1.41–7.22; $p = .007$). The risk of VTE increased with the number of the cardiovascular risk factors as follows: for two cardiovascular risk factors, the OR was 2.80 (95% CI, 1.22–6.72; $p = .001$); for three cardiovascular risk factors, the OR was 3.50 (95% CI, 1.22–10.15; $p = .001$); for four cardiovascular risk factors, the OR was 4.20 (95% CI, 1.14–11.23; $p = .002$).

Table 4. Simplified COMPASS–CAT Score for VTE prediction in ambulatory patients with common cancers on anti-cancer therapy

Predictors for VTE	Score[a]
Cancer-related risk factors	
Anti-hormonal therapy for women with hormone receptor-positive breast cancer or on anthracycline treatment	6
Time since cancer diagnosis $\leq$ 6 months	4
CVC	3
Advanced 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, 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

[a]Low/Intermediate risk: 0–6; high risk: $\geq$7.
Abbreviations: CVC, central venous catheter; VTE, venous thromboembolism.

Time since cancer diagnosis of less than 6 months (OR = 2.54, 95% CI, 0.84–2.43; p = .0001) and personal history of VTE (OR = 2.37, 95% CI, 0.93–2.73; p = .001) were also significant risk factors for VTE. The risk of VTE was significantly higher in patients with advanced or metastatic disease compared to those with localized disease (OR = 1.71, 95% CI, 0.92–1.83; p = .04).

Patients on anti-hormonal therapy for breast cancer had significantly higher VTE risk compared with those without (OR = 2.64, 95% CI, 0.82–2.23; p < .001). Anthracycline-containing chemotherapy was also an independent risk factor for VTE (OR = 5.33, 95% CI, 2.73–10.41; p = .0001)

The VTE risk was significantly higher in patients with partial remission or no response to treatment compared with those with complete remission (OR = 5.82, 95% CI, 1.22–11.24; p = .001).

Among the biomarkers, only platelet count higher than 350 $\times$ 10^9/L was significantly associated with the risk of symptomatic VTE (OR = 2.94, 95% CI, 0.93–3.01; p = .001).

Multivariate Analysis

The multivariate analysis showed that the following variables were significantly associated with the risk of VTE: anti-hormonal therapy (OR = 6.4, 95% CI, 3.16–12.96; p = .0001), hospitalization (OR = 5.41, 95% CI, 2.90–10.08; p = .0001), cardiovascular risk factors and comorbidities (OR = 5.18, 95% CI, 1.10–13.40; p = .0007), and time since cancer diagnosis $\leq$6 months (OR = 4.1, 95% CI, 2.10–7.98; p = .0001).

Hospitalization combined with anticancer treatment significantly increased the risk of VTE (OR = 8.4, 95% CI, 2.90–10.08; p = .013). Other significant VTE predictors were the presence of CVC (OR = 3.24, 95% CI, 1.56–6.72; p = .0015), platelet count $\geq 350 \times 10^9$/L (OR = 2.53, 95% CI, 0.92–2.64; p = .0038), anthracycline-containing chemotherapy (OR = 2.33, 95% CI, 1.02–5.33; p = .04), and an advanced stage of cancer (OR = 1.93, 95% CI, 0.92–2.64; p = .0048). Cancer evolution was strongly and significantly associated with the stage.

Table 3 shows the relative risk and the 95% CIs of variables, which, according to the multivariate regression, were significantly associated with the risk of VTE.

Derivation of the Risk Assessment Model

The entire population evaluable after 6-months follow-up was 1,023 patients. The dependent variable is the VTE risk and all predictors are binary: 1 (Yes) or 0 (No). Multivariate logistic analysis led to the following equation:

*VTE risk = −5.4876 + (1.6876*Hospitalization) + (1.6441* At least two cardiovascular risk factors or comorbidities) − (0.6963*Advanced stage of cancer) + (1.8565* Anti-hormonal therapy or anthracycline-containing therapy) + (1.1768*CVC) + (1.4108*Time since cancer diagnosis ≤6 months) + (0.9274* Platelet count ≥ 350 × 10^9/L) + (0.3726*Personal history of VTE)*

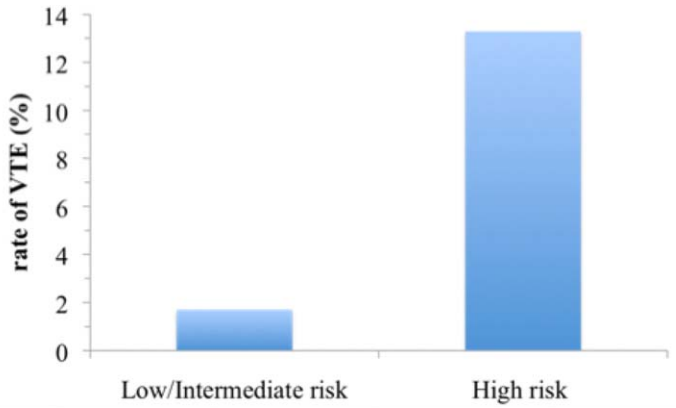
To simplify the model, a score was formulated by calculating an integral numeric value for each predictor according to the degree of its significance stemming from the multiple regression coefficients (Table 4).

The model stratified patients into high and low/intermediate risk for VTE. Accordingly, the cut-off values for the stratification of patients using the COMPASS–CAT RAM and the simplified COMPASS–CAT score are shown in Figure 2. For each separate type of cancer, the distribution of VTE events in the high and low/intermediate risk groups was similar to that in the total population (Fig. 2).

Qualitative Characteristics of Risk Assessment Model

The model and the score at the cut-off value for high risk level (>-4.7 and $\geq$7, respectively), had a NPV of 98% and a PPV of 13%. The sensitivity and the specificity of the COMPASS–CAT RAM was 88% and 52%, respectively. According to the Hosmer-Lemeshow test, a p = .23 showed that the model was well calibrated. Plotting the expected VTE events, according to the model, against the observed VTE events, as well as the expected against the observed number of patients without any VTE event, confirmed the good calibration of the model (r^2 = .99; Fig. 3). The ROC curve was plotted to evaluate the discrimination power of the model between the high-risk and the low-/intermediate-risk population for VTE. The AUC was 0.85, indicating very good discrimination capacity.

An alternative model derived after the elimination of breast cancer patients from the derivation cohort had the same predictors and similar qualitative characteristics as the initial COMPASS–CAT RAM. The inclusion of patients with CVC thrombosis into the derivation cohort as well as the elimination of the patients who received prophylaxis with enoxaparin after enrollment in the study did not bias the accuracy of the model because the alternative models developed according to these scenarios were less accurate than the COMPASS–CAT RAM (data not shown).



VTE risk level	Ranges of COMPASS-CAT RAM (min–max)	Ranges of COMPASS-CAT Score (min–max)	VTE events (*n*)	Rate of VTE
Low/Intermediate risk (*n* = 506)	<-4.8	0 to 6	9 *Breast cancer: 6* *Colorectal cancer: 2* *Lung cancer: 0* *Ovarian cancer: 1*	1.7%
High risk (*n* = 517)	>-4.7	≥7	69 *Breast cancer: 45* *Colorectal cancer: 14* *Lung cancer: 5* *Ovarian cancer: 5*	13.3%

Figure 2. Incidence of VTE according to the stratification of patients to risk levels using the COMPASS–CAT RAM and the simplified score. The number of VTE events per type of cancer in each level of risk is shown.

Abbreviations: COMPASS–CAT RAM, COMPASS–CAT risk assessment model; VTE, venous thromboembolism.

Discussion

A new RAM for VTE applicable to outpatients after the initiation of anticancer treatment for common solid tumors was derived from the prospective COMPASS–CAT study. The COMPASS–CAT RAM includes VTE risk factors related to patient characteristics and comorbidities as well as variables related to the cancer and its treatments. The COMPASS–CAT RAM is composed of well-defined and easily collected predictors that provide a global evaluation of VTE risk. The COMPASS–CAT RAM can be applied to outpatients at any time after treatment initiation during the patient's anticancer therapy. The predictors used in the model are as follows: (a) recent hospitalization (<3 months), (b) cardiovascular risk factors, (c) stage of cancer, (d) anti-hormonal therapy for women with breast cancer or anthracycline-containing chemotherapy, (e) presence of a CVC, (f) time since cancer diagnosis, (g) platelet count $\geq 350 \times 10^9$/L, and (h) personal history of VTE. The model stratifies patients into high and low/intermediate levels of VTE risk. The multinational design of the study, which is one of its strengths, allowed the identification of the impact of both cancer-related and patient-related risk factors and, therefore, this simple RAM responds to the generalizability criteria for risk assessment tools [26, 27].

In the first part of the study, the most clinically relevant risk factors of VTE were identified, and subsequently the RAM was developed using data from the first 6 months of follow-up because the vast majority of thromboembolic events occurred within this interval. We demonstrate herein that hospitalization within the last 3 months prior to assessment is an independent risk factor for VTE in outpatients who are on therapy for one of the studied cancers. This finding is in agreement with the data reported by a recently published population-based case-control study [30]. We also show that after initiation of anticancer treatment, patient-related risk factors are major determinants for the risk of CAT. Indeed, cardiovascular risk factors and/or cardiovascular comorbidities were associated with a fivefold increase of VTE risk. Noteworthy, VTE risk further increases when multiple cardiovascular risk factors and comorbidities are present. Overweight or obesity and the personal history of thrombosis are also independent VTE risk factors. Among cancer-related variables, the univariate analysis showed that the predictor "time since cancer diagnosis," which refers to the time elapsed between assessment and cancer diagnosis, figures among the major risk factors for VTE. Indeed, patients with cancer diagnosed within 6 months prior to assessment had 2.5-fold higher VTE risk as compared with those for whom this interval period was longer than 6 months. The risk of VTE was about twofold higher in patients with advanced cancer disease compared with those with localized stage, and it was independent of the therapeutic strategy. Anti-hormonal treatment (to women with breast cancer) or anthracycline-containing chemotherapy were independent risk factors for VTE. Interestingly, the presence of CVC was found to be an independent risk factor for VTE. However, the design of the present study does not allow a precise evaluation of the impact of the CVC on the risk for DVT and/or PE. The concept that the risk imparted by CVC is also systemic is supported by the data reported by Ashrani et al. [30]. Patients with partial remission or refractory disease had almost sixfold higher VTE risk compared with those with complete remission. Lastly, a platelet count higher than 350×10^9/L was associated with a significant increase of VTE risk in agreement with previous reports [17].

Following this analysis, a new RAM was constructed. The derivation of the model was carried out for the entire cohort of

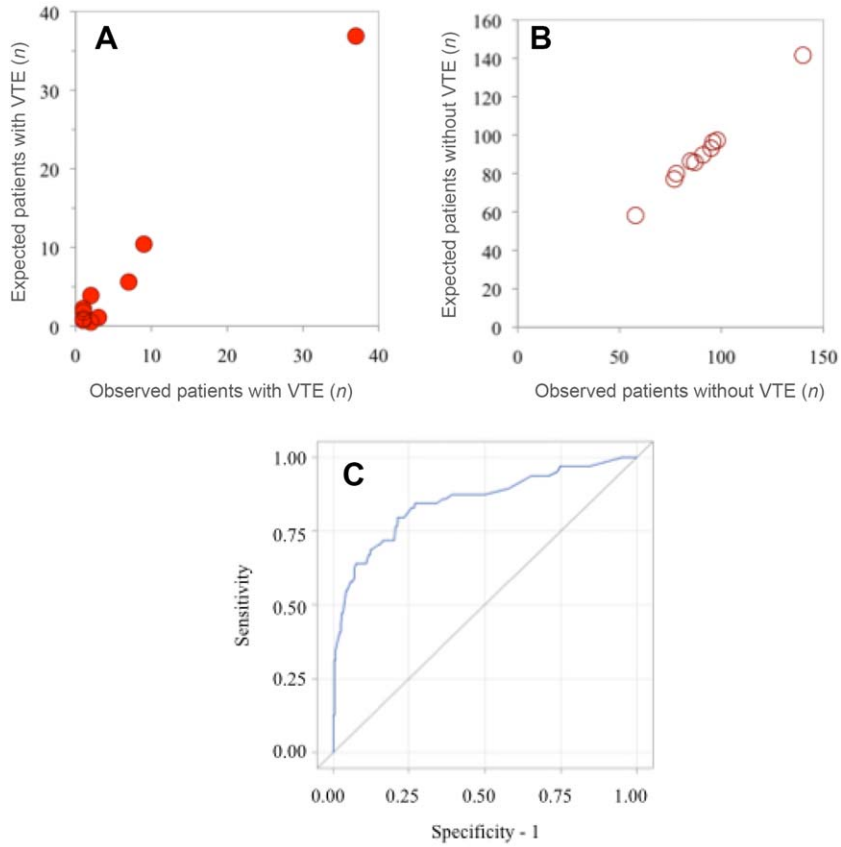


Figure 3. Qualitative characteristics of the COMPASS–CAT RAM: correlation between the expected and the observed number of patients with VTE **(A)** and without VTE **(B)** ($r^2 = .99$). The cohorts of patients were stratified into ten groups. Each point depicts the number of the expected and observed events patients in each group. The ROC analysis of the model **(C)** in the derivation cohort (area under the curve = 0.85).

Abbreviations: COMPASS–CAT RAM, COMPASS–CAT risk assessment model; ROC, receiver operating characteristics; VTE, venous thromboembolism.

evaluable patients according to the methodology proposed by Hendriksen et al. [26]. The procedure for model derivation follows the rule of thumb, the so-called EPV 1–10, and provides a reliable prediction capacity [27, 28].

The COMPASS–CAT RAM leads to the stratification of patients with breast, colorectal, lung, or ovarian cancers into a high-risk level for VTE, where the rate of thrombotic events is 13%, and low-/intermediate-risk level for VTE, where the rate is 1.7%. This RAM is particularly efficient to rule out cancer patients at low or intermediate thrombotic risk because it has a NPV of 98%. The sensitivity and specificity of this model are 88% and 52%, respectively. The use of regression coefficients warrants the accuracy of the model but limits its applicability for electronic scoring systems supported by advanced calculation power. Acknowledging this restriction, a simplified score was developed that has the same performance with the model. The proposed strategy will allow the application of the score at health care structures where powerful electronic calculators are not available.

The derivation cohort for COMPASS–CAT RAM had characteristics that could potentially introduce some bias on the accuracy of the score. The patients who received thromboprophylaxis with LMWH after enrollment in the study were excluded from the cohort. Administration of thromboprophylaxis to these patients allows the assumption that they were classified to a highest risk level by the treating physicians and thromboprophylaxis with enoxaparin suppressed the thromboembolic risk. As a consequence, their inclusion in the cohort may lower the accuracy and qualitative characteristics of the model. This analysis showed that the accuracy of the COMPASS–CAT RAM was lower in outpatients who, according to the clinical evaluation of the treating physician, were classified at high VTE risk and received thromboprophylaxis. This RAM is complementary in the clinical decision when the awareness for VTE risk is increased. The presence of patients with CVC thrombosis in the derivation cohort might introduce some bias in the accuracy of the model because the risk of this particular thrombosis is also influenced by factors related to the anatomical localization and the procedure of catheter insertion [31]. The alternative models derived from a cohort without these patients included some of the main predictors of the COMPASS–CAT RAM but had significantly lower predictive power and demonstrated poorer qualitative characteristics compared with the original model. Finally, the patients with breast cancer, who were about 60% of the derivation cohort, did not introduce any bias to the predictive power of the model when it was applied to the patients with lung, ovarian, or colon cancer (data not shown).

External validation is the optimum strategy to control the accuracy of predictive models. The split-sample method or the retrospective analysis of an existing database are the most commonly used procedures for validation of RAMs. Nevertheless, these methods are not optimal because they are

vulnerable to hazardous effects of the cohort composition, and for this reason, they were not used in the present study. However, we applied the split sample method for internal validation of the RAM and we confirmed its validity (data not shown). The absence of a validation cohort is an evident limitation of our study that imposes the need for external validation as a prerequisite for its routine use in clinical practice. However, the prospective design of the study is a strength for the derivation of this new RAM. Incidental VTE was not systematically assessed in patients enrolled in the study; therefore, this variable was not included in the analysis. This might represent a limitation on the accuracy of the COMPASS–CAT RAM. An additional limitation of the present study is that the number of VTE events in lung cancer patients was unusually low, allowing for the hypothesis that some thromboembolic events were missed at diagnosis or that others could be associated with fatal PE and thus contributed to the mortality.

The COMPASS–CAT RAM targets patients with common solid cancer who are receiving anticancer treatment, whereas the Khorana score is applicable in patients at the initiation of the chemotherapy. Patients with breast cancer represent about 60% of the whole study population, reflecting the real-life situation that this is the most frequent type of cancer in the community. Almost all patients enrolled in the derivation cohort were already on chemotherapy, allowing for the application of the RAM after the initiation of the anticancer treatment. This is an advantage of the COMPASS–CAT RAM considering that the awareness for VTE risk is rather low among oncologists, and therefore, the probability of missing an evaluation of VTE risk before treatment initiation is high [32, 33]. Many patients in the derivation cohort who experienced VTE had symptomatic distal DVT. Although some authors have questioned the clinical relevance of distal DVT, and the proximal DVT is preferred as the endpoint in clinical studies, we should underline that cancer patients who experience isolated symptomatic distal DVT are at high risk of recurrence [34–36]. Moreover, according to the international recommendations, the therapeutic strategy for cancer-associated distal DVT is not different when compared with proximal DVT [12–14]. As a consequence, the ensemble of the clinical endpoints defined in the study represents common features of CAT and allows a wider RAM applicability.

Conclusion

The prospective COMPASS–CAT study provides a new, accurate RAM for VTE in outpatients on anticancer treatment for common solid tumors that allows stratification of patients at high and low/intermediate risk for VTE. The originality of this RAM is that it includes reliable and easily collected VTE predictors associated with cancer evolution and its treatments as well as with patient characteristics and comorbidities. It is applicable for patients suffering the most frequent types of solid tumors, which have major impact on VTE burden, and it can be applied while the patient is on chemotherapy, thus permitting re-evaluation of VTE risk during the patient's journey. It has been derived from a cohort of patients who were prospectively recruited and followed, and this provides its robustness. The COMPASS–CAT RAM can easily identify cancer patients on anticancer treatment at low or intermediate risk of VTE and rule out the need for an antithrombotic primary prevention strategy. An independent validation of the COMPASS–CAT RAM should allow its routine use in clinical practice.

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Disclosures

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