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ORIGINAL ARTICLE

Utility of the Khorana and the new-Vienna CATS prediction scores in cancer patients of the HYPERCAN cohort

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Abstract

Background: Risk assessment models (RAMs) are relevant approaches to identify cancer outpatients at high risk of venous thromboembolism (VTE). Among the proposed RAMs, the Khorana (KRS) and the new-Vienna CATS risk scores have been externally validated in ambulatory patients with cancer.

Objectives: To test KRS and new-Vienna CATS scores in 6-month VTE prediction and mortality in a large prospective cohort of metastatic cancer outpatients during chemotherapy.

Patients/Methods: Newly diagnosed patients with metastatic non-small cell lung, colorectal, gastric, or breast cancers were analyzed (n = 1286). The cumulative incidence of objectively confirmed VTE was estimated with death as a competing risk and multivariate Fine and Gray regression.

Results: Within 6 months, 120 VTE events (9.7%) occurred. The KRS and the new-Vienna CATS scores showed comparable c-stat. Stratification by KRS provided VTE cumulative incidences of 6.2%, 11.4%, and 11.5% in the low-, intermediate-, and high-risk categories, respectively (p = ns), and of 8.5% vs. 11.8% (p = ns) in the low- vs. high-risk group by the single 2-point cut-off value stratification. Using a pre-defined 60-point cut-off by the new-Vienna CATS score, 6.6% and 12.2% cumulative incidences were obtained in the low- and high-risk groups, respectively ($p < 0.001$). Furthermore, having

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a KRS ≥2 = or a new-Vienna CATS score >60 points was also an independent risk factor for mortality.

Conclusion: In our cohort, the 2 RAMs showed a comparable discriminating potential; however, after the application of cut-off values, the new-Vienna CATS score provided statistically significant stratification for VTE. Both RAMs proved to be effective in identifying patients at increased risk of mortality.

KEYWORDS
cancer, metastatic, risk assessment, thromboembolism, thrombosis

1 | INTRODUCTION

Venous thromboembolism (VTE) is a frequent complication in patients with active cancer who have a 9- to 12-fold higher VTE risk in the first 6 months after diagnosis than patients without cancer [1,2]. The most frequent VTE events in cancer include deep vein thrombosis (DVT) of the lower limbs and pulmonary embolism (PE). In addition, an increased rate of VTE in atypical sites, including visceral or splanchnic vein thrombosis has been reported.

The overall incidence of VTE in cancer continues to increase over time, due to the increased detection by imaging for staging purposes, the use of thrombogenic anticancer therapies, and longer survival of patients [1]. It has been estimated that 20% of all first VTE events occur in patients with active cancer [2,3], particularly in those with breast, prostate, colon, and lung cancer, reflecting the high prevalence of these malignancies in the general population (approximately 40-50% of all cancers) [4].

VTE occurrence carries important consequences for these patients, such as increased morbidity, the use of anticoagulant therapies, increased risk of thrombotic recurrences and bleeding complications during anticoagulation, delays in anticancer therapies, and increased health care costs [5,6]. Most importantly, VTE impacts cancer mortality [7,8]. For all these reasons, the prevention of cancer-associated VTE is very important. Current guidelines recommend primary thromboprophylaxis in patients with cancer admitted to the hospital for acute medical illnesses [9–11], but a significant proportion of thrombotic events occur in the outpatient setting, mainly in the first months after cancer diagnosis and during the administration of antitumor therapies [12]. For these patients, current guidelines do not recommend routine pharmacological thromboprophylaxis, except for patients with multiple myeloma treated with immunomodulatory imide drugs and for patients considered at high VTE risk. In this respect, large differences exist in the VTE risk levels among different types of cancer, and also within the same type, being influenced by several factors, including those related to the malignant disease (i.e., tumor type, clinical stage, anticancer therapies, use of erythropoietic stimulating agents, insertion of central venous lines), and those related to the individuals (i.e., gender, race, age, previous VTE history, immobilization, obesity) [13].

To identify non-hospitalized patients with cancer at high VTE risk, several models of thrombotic risk assessment (RAMs), combining both clinical and laboratory parameters, have been developed [9]. The use of the Khorana risk score (KRS), the best-known and validated model, has been included in recent guidelines [14,15] to help identify patients at high risk of cancer and eligible for thromboprophylaxis. The variables included in the KRS are the cancer type, the prechemotherapy leukocyte and platelet counts, hemoglobin level or use of erythropoietic stimulating agents, and body mass index (BMI) [16]. However, the predictive capacity of the KRS is not effective in several situations [17–19]. Starting from the KRS, other RAMs have been developed [20–25]. Among these, the new-Vienna CATS score by Pabinger et al.

Essentials

- Risk assessment models are recommended for identifying cancer outpatients at high risk of venous thromboembolism.
- The Khorana risk and the new-Vienna CATS scores are tested in the HYPERcoagulation in CANcer metastatic cohort.
- The new-Vienna CATS score significantly categorizes patients at higher venous thromboembolism risk.
- Both scores effectively identify patients at higher risk of mortality at 6 months.

[25] appears particularly attractive because it is based on only 2 parameters, i.e., the tumor site and D-dimer levels, and has been externally validated.

Interestingly, these RAMs are also under active investigation for their capacity to predict cancer outcomes other than VTE, and some studies have recently shown the ability of KRS to identify patients with cancer at high risk of death [26–28]. The prognostic role of D-dimer in cancer has not yet been defined for all types of cancer [29].

In the frame of the HYPERcoagulation and CANcer (HYPERCAN) study, a prospective observational Italian multicenter study, we enrolled patients with a new diagnosis of metastatic cancer with 4 of the most prevalent tumor types, i.e., non-small cell lung (NSCLC), gastric (GC), colorectal (CRC), and breast (BC) cancers for whom systemic chemotherapy was indicated [30]. In this large prospective cohort of cancer patients, we aimed to describe the incidence of objectively confirmed VTE and evaluate the discriminatory performance of the 2 validated RAMs (KRS and the new-Vienna CATS scores) for the identification of high VTE-risk subjects. In addition, we aimed to evaluate the performance of the 2 RAMs to predict mortality at 6 months in the same group of patients.

2 | MATERIALS AND METHODS

2.1 | Study design and patients' population

The HYPERCAN study prospectively enrolled adult patients of both genders with either limited or metastatic NSCLC, CRC, GC, and BC [30]. In this analysis, we included the cohort of patients (n = 1512) with metastatic disease (TxNxM1) scheduled for systemic chemotherapy enrolled from April 2012 to the end of December 2019. Exclusion criteria at enrollment were acute medical illnesses, hospitalization, life expectancy <3 months, treatment for VTE, Eastern Cooperative Oncology Group Performance Status ≥3. From this cohort, 226 patients were excluded from the analysis for the following reasons: 64 had a histopathological diagnosis other than NSCLC, CRC, BC, or GC, 54 were lost at follow-up, and 6 withdrew informed consent. An additional 102 patients were excluded because of the unavailability of baseline blood samples. Therefore, 1286 patients were eligible for this analysis, with a median observation time of 414 days (5th-95th: 46-1,811 days). Patients were recruited at the oncological units of the following Italian Institutions: Humanitas Clinical Institute (Rozzano, Milano), Hospital Papa Giovanni XXIII (Bergamo), Istituto Nazionale Tumori (Milan), Hospital San Filippo Neri (Rome), Policlinico San Marco (Zingonia, Bergamo), Hospital Treviglio-Caravaggio (Treviglio, Bergamo), Hospital San Giovanni Addolorata (Rome), and Cancer Institute Giovanni Paolo II (Bari). For all study subjects, data recorded at enrollment were: age, gender, cancer type and histopathology, biological characteristics according to the type of tumor, BMI, history of smoking, current medications, Eastern Cooperative Oncology Group Performance Status, relevant comorbidities, anticancer treatment, previous thrombosis history (both arterial and venous), baseline use of anticoagulants, presence of central venous catheter (CVC), and recent surgery (<30 days from enrollment). According to the study protocol, after enrollment, patients were followed-up for at least 5 years. The collection of blood samples was scheduled at enrollment, before starting systemic chemotherapy, and at each visit planned. During follow-up, information on any administered treatment, thrombosis, bleeding, clinical response, disease progression, and overall survival (OS) were recorded.

2.2 | Ethical statement

The study protocol was been approved by the local Ethics Committee (Comitato Etico della Provincia di Bergamo, del. 146, February 1, 2012). All participants provided informed written consent that was also obtained for data recording, collection, and storage of blood samples, to allow regulatory monitoring, statistical analysis, and publication of results. The ethical conduct of the study is regulated by the last revision of the Helsinki Declaration. The study was coordinated in the Department of Immunohematology and Transfusion Medicine, Papa Giovanni XXIII Bergamo Hospital, Italy.

2.3 | Outcome measures

The primary outcome measure of the current analysis is the occurrence of the first symptomatic or incidental VTE at 6 months from the start of treatment, objectively confirmed by using duplex sonography, phlebography, computerized tomography, or ventilation-perfusion lung scan. VTE includes symptomatic DVT, symptomatic non-fatal PE, fatal PE, incidental proximal DVT (popliteal vein or higher), incidental proximal PE (segmental arteries or larger), and symptomatic CVC related. Incidental PE or DVT is defined as asymptomatic thrombi that are incidentally reported during imaging performed for cancer staging. Only events confirmed and validated by the Independent Central Adjudication Committee were included in the analysis. The OS at 6 months from enrollment was considered as a secondary outcome. In addition, the OS time was defined as time from enrollment until death, whatever the cause.

2.4 | D-dimer

Plasma levels of D-dimer were measured by an automated, quantitative immuno-turbidimetric assay (STA Liatest D-Di PLUS, Stago, France) on a STAR R Max3 analyzer (Stago) according to the manufacturer's instructions. Levels of D-dimer are expressed as μg/mL, the detection limit is 0.27 μg/mL, and the clinical cut-off is 0.5 μg/mL (CV% intra-assay: 7.31%; CV% inter-assay: 6.27%). The measurement of the D-dimer was performed in the laboratory of Bergamo Hospital.

2.5 | Statistical analysis

Categorical variables were reported as frequencies and proportions, whereas continuous variables were reported as median and 5th to 95th percentile ranges. Differences between groups were tested by Mann–Whitney test for quantitative variables, and by the chi-squared test for categorical variables. The cumulative incidence of VTE was estimated with death as a competing risk, and multivariate Fine and Gray regression [31] was used to obtain the relative subdistribution-hazard ratio (SHR) between VTE risk categories, corrected for the confounder, i.e., "the use of anticoagulation," in both KRS and new-Vienna CATS scores. The survival function for OS was estimated using the Kaplan–Meier method. Multivariate Cox proportional hazard regression was performed to evaluate the performance of KRS and CATS scores in predicting 6-month OS. The score discriminatory ability for both outcomes was also assessed with the area under the receiver operating characteristic (ROC) curve (AUC). A calibration plot was used to provide measures of the models' calibration.

2.6 | KRS calculation

To calculate the KRS, we used clinical and complete blood cell count data collected at enrollment in the study before starting chemotherapy. According to the KRS, 1 point is assigned to each of the following categories: platelet count $>350 \times 10^9$/L, leukocyte count $>11 \times 10^9$/L, hemoglobin <10 g/dL or the use of erythropoietin stimulating agent, and a BMI $\geq$35 kg/m^2. Tumor-site risk category adds 2 points for GC and 1 point for NSCLC. Patients were then classified as "low-risk" (0 points), "intermediate-risk" (1–2 points), and "high-risk" ($\geq$3 points) [2]. Because a recent meta-analysis demonstrated that a single cut-off value of 2 points is preferable for discriminating patients in 2 categories only, i.e., high- ($\geq$2 points) and low-intermediate risk (<2) [17], we also tested this type of stratification in our cohort of patients [32,33]. The same single cut-off was applied to identify patients at a high risk of mortality at 6 months.

2.7 | New-Vienna CATS score calculation

The published formula of the new-Vienna CATS score [25] was used to calculate the individual VTE risk, which is based on tumor site and D-dimer as a continuous variable, as follows: *6-month VTE risk (%) = 100*(1-(1-0.02137053)* $^{e\ (0.6709158 * cancer\ site + 0.2793001 * log_2(ddimer+1))}$. According to the score, GC is considered at very high risk, NSCLC and CRC at high risk, and BC at low risk for VTE. The 5% probability of risk was used as a cut-off value to discriminate patients at high- and low-VTE risk, which corresponds to a score of 60 points by the nomogram reported by Pabinger et al. [25,34]. The same cut-off value was also used for prediction of mortality risk at 6 months of follow-up.

3 | RESULTS

3.1 | Baseline characteristics of the study population

Of the 1512 subjects who comprised the HYPERCAN cohort of patients with metastatic cancer, 1286 patients were eligible for the present analysis (Figure 1). The characteristics of the study population at enrollment are shown in Table 1. All patients were Caucasian, with a median age of 65 years and 55% were male. The most represented tumor type was NSCLC (40%), followed by CRC (34%), BC (14%), and GC (12%). A total of 489 patients (38%) had an implanted CVC at enrollment (8.5% of NSCLC, 71.4% of CRC, 23.5% of patients with BC, and 64.6% of patients with GC). The type of CVC was a port-a-cath in 62%, a Groshong line in 16%, and a peripherally inserted central catheter in the remaining 22% of patients.

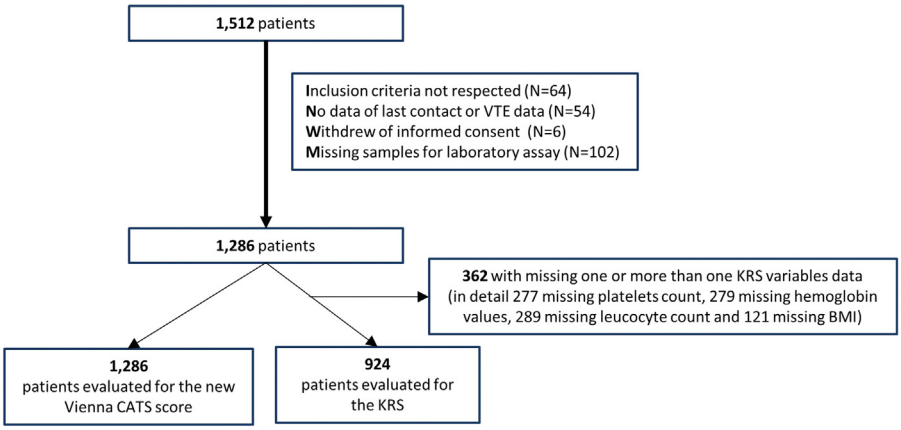
Approximately 60% of patients presented at least one cardiovascular risk factor, including smoking, hypertension, hypercholesterolemia, diabetes, or BMI $\geq$35 kg/m^2. According to the BMI classification, 5.7% of patients were underweight, 54% were normal weight, and 30% overweight, whereas 10.5% were obese (8.3% were class I, 1.9% were class II, and 0.3% were class III); patients with GC had significantly ($p < 0.001$) lower median BMI than others. Forty-one subjects (23 males and 18 females; age range 49-82 years) had atrial fibrillation (AF): 38 were receiving a prophylactic dose of low–molecular-weight heparin (LMWH) and 3 were receiving aspirin. Before enrolment, the 38 patients on LMWH were receiving AF thromboprophylaxis with warfarin (n = 32) or with DOAC (n = 4). Treatments with LMWH and warfarin/DOAC were not concomitant. These treatments were switched to LMWH by the treating physicians at the start of chemotherapy, for simpler administration of fixed-dose LMWH without the need for PT-INR monitoring and the fear of potential drug-drug interaction (with direct oral anticoagulants). The 3 patients receiving aspirin continued with the same treatment. A previous history of VTE was recorded in 19 patients. At enrollment, 148 patients were taking antiplatelet drugs, whereas 64 were on prophylactic dose of LMWH (including the 38 with AF).

After enrollment, antitumor treatment was initiated for the patients (Table 1) as follows: 614 patients (47.7%) received platinum-based chemotherapy, 94 patients (7.3%) received platinum plus gemcitabine-based chemotherapy, 39 patients (3%) received anthracycline-based chemotherapy, 22 patients (1.7%) received gemcitabine-based chemotherapy, and 517 (40.3%) received other anticancer treatments (i.e., anthracycline-, taxan-, 5-fluorouracil-, irinotecan-, pemetrexed-, and vinorelbin-based chemotherapy regimens).

3.2 | Cumulative incidence of VTE

Within 6 months from study enrollment, 120 patients (70M /50F) experienced an objectively confirmed VTE. The median time to thrombosis was 68 days (Table 1), and approximately 75% of VTE

FIGURE 1 Study flowchart.



occurred within the first 3 months of the study. In the competing risk analysis, the 6-month VTE cumulative incidence among all patients was 9.7% (95% CI: 8.1-11.4) (Figure 2A), whereas according to the tumor site, it was 12.1% (9.4-15.2), 9.8% (7.2-12.8), 9.1% (5.1-14.6), and 3.4% (1.4-6.8) in patients with NSCLC, CRC, GC, and BC, respectively (Figure 2B).

The characteristics of patients with VTE are described in Table 1, and data are compared with those of patients who remained VTE-free during a similar time of observation. No statistically significant differences were observed in age, gender, BMI, hemoglobin, and leukocyte count between the 2 groups, whereas a significantly higher platelet count, a higher percentage of patients with NSCLC (49% vs. 33%), and a lower percentage of patients with BC (5% vs. 18%) were found in VTE than in the no-VTE group. In addition, patients with VTE showed significantly ($p < 0.001$) higher prechemotherapy plasma D-dimer levels.

As reported in Table 2, isolated DVT (45.8%) and isolated PE (42.5%) were the most frequent VTE types, followed by PE in association with DVT (11.7%). Most of VTE occurred in patients with NSCLC and CRC, followed by those with GC and BC. PE was fatal in 3 patients, 2 with NSCLC and 1 with BC. About half of the PE events were incidentally diagnosed by CT scan during cancer disease restaging. Fifteen cases of DVT were CVC-related and were localized in the brachial vein (n = 1), basilic vein (n = 1), subclavian vein (n = 3), jugular vein (n = 6), and vena cava (n = 4).

3.3 | VTE risk assessment according to KRS

Based on the information available at enrollment, the KRS was estimated in a subcohort of 924 subjects (i.e., 72% of the study population), 87 of whom developed VTE within 6 months of follow-up (9.4%). As reported in Figure 1, one or more parameters of the KRS were missing in the remaining 362 patients of the whole cohort, and therefore, they could not be included in the KRS calculation. Table 1 shows the main characteristics of these 924 patients that were comparable to those of the entire cohort, also for VTE incidence, i.e., 87 VTE/924 (9.4%) vs. 120 VTE/1286 (9.3%).

According to the cut-off values of leukocyte count adopted by the KRS (Table 1), a higher proportion of patients with leukocytes > 11×10^9/L (32.2% vs. 16.5%; $p = 0.000$) were present in VTE than in no-VTE group, and no significant differences were found in the other parameters of the score. Finally, 55.2% of patients in the VTE group had a KRS <2 (Table 1), and therefore classifiable as a low-risk patients.

The AUC of ROC curve analysis for the KRS as a continuous variable was 0.61 (95% CI: 0.55-0.67). The calibration plot showed that the model was adequately calibrated with no problems of methodical under- or overestimation of VTE (Supplementary Figure S1A). According to the original 3 risk group stratification of the score, the 6-month cumulative incidence of VTE was 6.2% (95% CI: 3.8-9.4) in the low, 11.4% (95% CI: 8.8-14.4) in the intermediate, and 11.5% (95% CI: 6.2-18.4) in high-risk group (Figure 3A). VTE cumulative incidences were statistically different between the intermediate vs. low-risk group, providing an SHR of 1.8 (95% CI: 1.1-3.1; $p = 0.024$), whereas no significant difference was found between high vs. low (SHR: 1.8; 95% CI: 0.89-3.85; $p = 0.094$) and intermediate vs. high (SHR: 1.02; 95% CI: 0.54-1.90; $p = 0.95$) risk groups. Dichotomous stratification according to the single cut-off value of 2 points provided a VTE cumulative incidence of 8.5% (95% CI: 6.4-11) vs. 11.8% (95% CI: 8.6-15.6) in the low- and high-risk categories, respectively, with no statistically significant difference among the 2 groups (SHR: 1.40; 95% CI: 0.92-2.14; $p = 0.11$) (Figure 3B). These data were also confirmed after the exclusion of the 64 patients on prophylactic anticoagulation. By ROC analysis, we searched for a more efficient KRS cut-off value in our cancer population. The analysis identified the 0 point as the best threshold value, and after stratification according to this cut-off, we found a cumulative incidence of 6.2% in the low-risk (KRS≤0) and of 11.4% in the high-risk (KRS>0) categories with a non-significant SHR ($p = 0.25$).

TABLE 1 Characteristics of the cancer patient's cohort.

	All patients (n = 1286)	VTE (n = 120)	No VTE (n = 892) [a]	p
Age, years median (min–max)	65 (27-92)	63 (38-85)	65 (27-92)	0.191
Gender Male, n (%)	702 (55)	70 (58)	456 (51)	0.141
BMI, kg/m^2[b]	24.1 (18.2-32.1)	23.9 (18.2-32.7)	24.2 (18.1-32.1)	0.905
CVC at enrollment, n (%)	489 (38.0)	51 (42.5)	353 (39.5)	0.381
CV risk factors (almost 1[#]), n (%)	774 (60)	38 (31.6)	378 (42.3)	0.025
D-dimer, ug/mL	0.8 (0.3-5.4)	1.2 (0.3-7.8)	0.6 (0.3-3.5)	0.000
Cancer type, n (%)				
NSCLC	510 (39.7)	59 (49.2)	299 (33.5)	
CRC	440 (34.2)	42 (35.0)	344 (38.6)	0.000
GC	153 (11.9)	13 (10.8)	93 (10.4)	
BC	183 (14.2)	6 (5.0)	156 (17.5)	
Blood cell count, median (IQR)[c]				
Hemoglobin, g/L	129 (96-155)	126 (95-150)	130 (98-157)	0.192
Leukocytes, 10^9/L	8 (4.2-16.2)	8.3 (3.3-22.5)	7.5 (4.1-14.9)	0.070
Platelets, 10^9/L	268 (145-509)	293 (140-521)	260 (148-509)	0.034
First-line chemotherapy, n (%)				
Platinum	614 (47.7)	63 (52.5)	429 (48.1)	
Anthracycline	39 (3.0)	2 (1.7)	23 (3.6)	
Gemcitabine	22 (1.7)	2 (1.7)	10 (1.1)	0.222[d]
Platinum + Gemcitabine	94 (7.3)	11 (9.2)	56 (6.3)	
Other	517 (40.3)	42 (35.0)	365 (40.9)	
Khorana score items, n (%)				
Number of patients	924	87	647	
Hemoglobin <100 g/L	72 (7.8)	9 (10.3)	37 (5.7)	0.095
Leukocytes count ≥11 × 10^9/L	204 (22.1)	28 (32.2)	107 (16.5)	0.000
Platelet count ≥350 × 10^9/L	225 (24.4)	23 (26.4)	133 (20.6)	0.208
BMI ≥35 kg/m^2	17 (1.8)	3 (3.4)	12 (1.9)	0.323
Khorana score, n (%)				
Number of patients	924	87	647	
0 point	294 (31.8)	18 (20.7)	251 (38.8)	
1 point	283 (30.6)	30 (34.5)	197 (30.4)	0.023
2 points	234 (25.3)	27 (31.1)	148 (22.9)	
≥3 points	113 (12.3)	12 (13.7)	51 (7.9)	

BC, breast cancer; BMI, body mass index; CVC, central venous catheter; CV, cardiovascular; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; GC, gastric cancer; VTE, venous thromboembolism.

[a] Patients with almost 6 months of follow-up. *p* = statistical significance VTE vs. no VTE groups.

[#] Smoking, hypertension, hypercholesterolemia, diabetes, or BMI ≥35 kg/m^2.

[b] BMI values were available for 1165 patients.

[c] Hemoglobin values were available for 1007 patients, leukocyte count for 997, and platelet counts for 1009.

[d] Due to the low number of patients on anthracycline alone (n = 2) and gemcitabine alone (n = 2) in the VTE group, these patients were incorporated into the other group for the estimate of statistical significance.

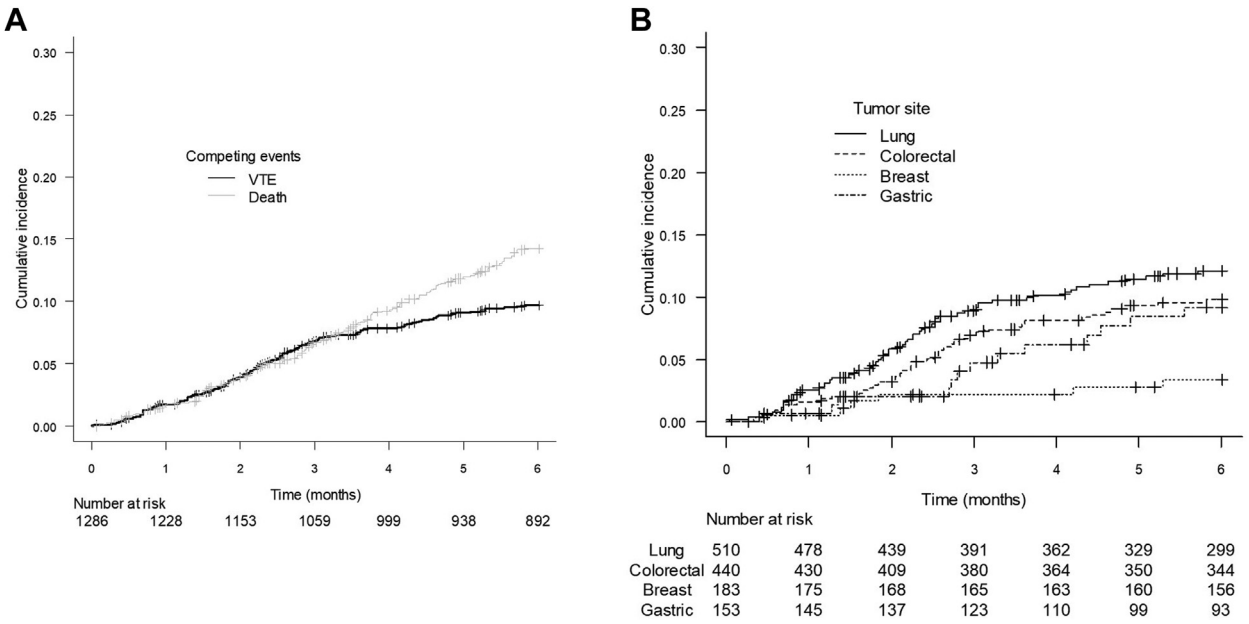


FIGURE 2 Cumulative incidence of venous thromboembolism during 6 months from enrollment (**A**). The gray line is the corresponding estimate of the competing event. Cumulative incidence of venous thromboembolism with death as a competing risk according to the tumor site (**B**).

3.4 | VTE risk assessment according to the new-Vienna CATS score

The new-Vienna CATS score was estimated both in the cohort of 924 patients tested for the KRS as well as in the entire cohort of 1286 patients. The stratification of the 924 patients with the 60-point, cut-off value provided VTE cumulative incidences of 7.3% (95% CI: 5.0-10.1) and 11.7% (95% CI: 9.1-14.7) in the low- and high-risk categories, respectively, with a statistically significant SHR of 1.7 (95% CI: 1.1-2.6; $p = 0.023$). Likewise, the stratification of all 1286 patients resulted in VTE cumulative incidences of 6.6% (95% CI: 4.8-8.9) and 12.2% (95% CI: 9.9-14.8) in the low- and high- risk categories, respectively, with a still statistically significant SHR of 1.9 (95% CI: 1.3-2.8; $p < 0.001$) (Figure 3C). ROC analysis considering the score as a continuous variable showed an AUC of 0.62 (95% CI: 0.56-0.68) for the cohort of 924 patients and 0.66 (95% CI: 0.61-0.71) for the entire cohort. Calibration plot of the model showed agreement between predicted VTE risks and observed VTE incidences (Supplementary Figure S1B). Interestingly, the percentage of low-risk patients in the VTE group by the new-Vienna CATS score was lower (33.3% in the 924 patients and 30.8% for the whole cohort) than that found by the KRS (55.2%).

All these data were also confirmed after the exclusion of the 64 patients on prophylactic anticoagulation.

TABLE 2 Type and frequencies of venous thromboembolism (VTE).

	Total VTE (n = 120)	NSCLC (n = 59)	CRC (n = 43)	GC (n = 13)	BC (n = 6)
Pulmonary embolism (PE)	51 (42.5)	28 (47.4)	15 (35.7)	-	1 (16.7)
Symptomatic	20 (39.2)	10 (35.7)	7 (46.6)	-	-
Incidental	28 (54.9)	16 (57.1)	8 (53.4)	-	-
Fatal	3 (5.9)	2 (7.2)	-	-	1 (100)
Deep vein thrombosis (DVT)	55 (45.8)	23 (39)	22 (52.4)	7 (53.8)	3 (50)
Lower limbs	23 (41.8)	12 (52.2)	6 (27.3)	2 (28.6)	3 (100)
Upper extremity	10 (18.2)	8 (34.8)	-	2 (28.6)	-
Vena cava	5 (9.1)	-	5 (22.7)	-	-
Portal vein	3 (5.5)	-	3 (13.6)	-	-
Mesenteric vein	5 (9.1)	-	5 (22.8)	-	-
Jugular vein	8 (14.5)	2 (8.7)	3 (13.6)	3 (42.8)	-
Renal vein	1 (1.8)	1 (4.3)	-		
DVT + PE	14 (11.7)	8 (13.6)	5 (11.9)	6 (46.2)	2 (33.3)

Data are expressed as numbers (%).

BC, breast cancer; CRC, colorectal cancer; DVT, deep vein thrombosis; GC, gastric cancer; NSCLC, Non-small cell lung cancer; PE, pulmonary embolism; VTE, venous thromboembolism.

3.5 | Mortality risk prediction

After a median follow-up of 414.5 days, 807 deaths were registered, with 199 of them occurred within 6 months from enrollment. The corresponding 6-month OS was 84% (95% CI: 82-86). According to the tumor site, the mortality rate was higher in the group of patients with NSCLC (23.1%) and GC (21.6%) than that for patients with BC (7.7%) and CRC (7.7%). By ROC analysis, the AUC for 6-month mortality was 0.69 (95% CI: 0.65-0.74) for the KRS and 0.68 (95% CI: 0.64-0.71) for the new-Vienna CATS score. Starting from the KRS, the

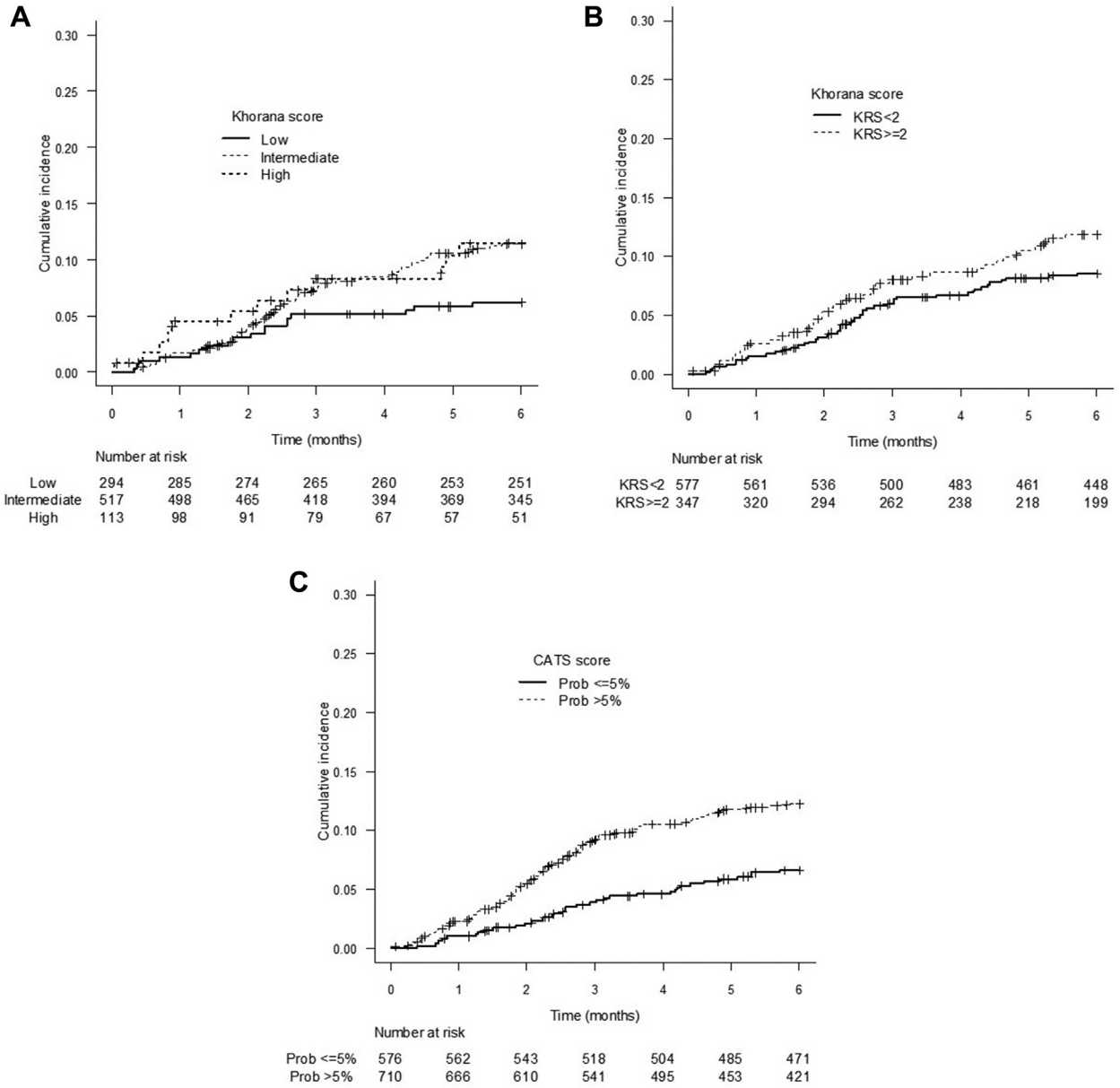


FIGURE 3 Cumulative incidence of 6-month venous thromboembolism with death as the competing risk among patients with cancer according to the original 3 risk categories stratification (low, intermediate, and high) of the Khorana risk score (**A**), the dichotomous stratification by the single cut-off value of 2 of the Khorana risk score (**B**), and the dichotomous stratification by the cut-off value of 60 points of the new-Vienna CATS score (**C**).

stratification according to the cut-off value of 2 provided a cumulative incidence of mortality of 9.9% (95% CI: 7.7-12.7) in patients with a KRS <2 and of 26% (95% CI: 21.6-31.2) in patients with KRS ≥2 (hazard ratio: 2.9; 95% CI: 2.1-4.0; $p < 0.000$) (Figure 4A). By the new-Vienna CATS score, the cumulative incidence of 6-month mortality was 7.4% (95% CI: 5.5-9.9) in the group of patients with a score ≤60 and 23.9% (95% CI: 20.8-27.4) in the group with a score >60 (hazard ratio: 3.57; 95% CI: 2.5-5.0; $p < 0.000$) (Figure 4B).

4 | DISCUSSION

In the present study, in a large prospective cohort of patients initiating a new chemotherapy regimen for a first diagnosis of metastatic NSCLC, CRC, BC, or GC [30], we estimated the 6-month incidence of VTE and evaluated the predictive value of 2 externally validated RAMs to test their effectiveness in identifying patients at low and high risk of VTE. Starting from a cohort of 1512 ambulatory patients with

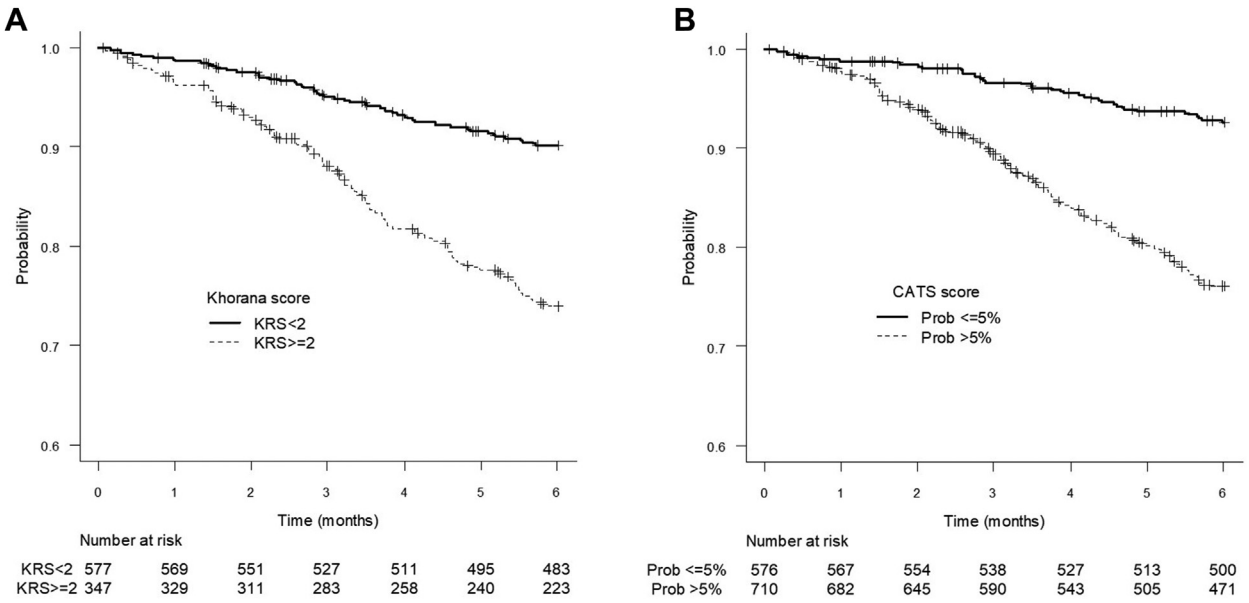


FIGURE 4 Kaplan–Meier plot illustrating overall survival among patients with cancer by the KRS using the cut-off value of 2 points (**A**) and by the new-Vienna CATS score using the cut-off value of 60 points (**B**).

cancer, we included a total of 1286 patients in the final analysis, with a median observation time of 414 days (5th-95th: 46–1811 days). Of these, 120 patients developed VTE within 6 months of enrollment while receiving chemotherapy. The median time to event was 68 days, and 75% of patients developed a VTE within the first 3 months of enrollment, a time window recognized as being at high-risk for VTE [35].

According to a competing-risk analysis, the cumulative risk of VTE at 6 months was 9.7% in the overall cohort and was the highest in NSCLC (12.1%) and the lowest in the BC (3.4%) group of patients, in agreement with published data [36]. The most frequent types of VTE were isolated DVT and isolated PE, accounting for 46% and 43% of total events, respectively, with approximately 55% of PE incidentally diagnosed during disease restaging. In recent years, incidental PE has become an important contributor to cancer-associated VTE rates in cancer outpatients [37], carrying the same recurrence risk and prognosis as CT-detected for suspected events [38–40]. All of our patients diagnosed with incidental VTE received anticoagulant therapy.

Overall, data from the HYPERCAN prospective cohort confirm the high incidence of VTE during chemotherapy in the setting of ambulatory cancer patients [14] and provide an opportunity to test the efficacy of validated RAMs in identifying patients at high risk of VTE in a cohort of newly diagnosed subjects, all with metastatic cancer disease of the most frequent types [30].

As a first step, we tested the ability of the KRS to significantly stratify our patients into different VTE risk categories, using both the original 3 (low, intermediate, and high) and the new proposed 2 (low and intermediate-high) levels of risk stratification. This analysis was performed in a subgroup of 924 patients, 362 subjects being excluded because some data on blood cell counts and/or BMI were missing. The results showed that no statistically significant difference in overall VTE rates between risk groups was found in our cohort. Indeed, according to the original 3 risk categories, the cumulative incidence of VTE at 6 months was 6.2% in the low, 11.4% in the intermediate, and 11.5% in the high-risk group: a statistically significant difference in the incidence of VTE was observed only between the low- vs. intermediate – risk categories. As reported by Khorana et al in 2008 [16], the use of the KRS in the derivation and validation cohorts, respectively, provided a VTE cumulative incidence of 0.8% and 0.3% in low-risk, 1.8% and 2.0% in intermediate-risk, and 7.1% and 6.7% in high-risk category. The use of the KRS to identify patients with a nearly 7% short-term risk of symptomatic VTE for studies of thromboprophylaxis was also been suggested by the authors. Our findings on the application of the KRS in the HYPERCAN cohort are very different, since the VTE cumulative incidence obtained in the low-risk patients is 6.2%, which is very close to that of high-risk categories of the Khorana derivation and validation cohorts (i.e., 7.1 and 6.7%). A VTE incidence of 6.2% in the HYPERCAN low-risk group indicated that these patients still carry a substantial risk of VTE.

On the other hand, it should be considered that our incidence of VTE in the low-risk KRS group is in line with data from a recently published meta-analysis [17], which evaluated the performance of the KRS in 55 cohorts enrolling 34,555 cancer outpatients and that it also incorporated studies evaluating incidentally detected VTE as an outcome event. Results from this meta-analysis showed a cumulative incidence of VTE of 5.0% (95% CI: 3.9-6.5), 6.6% (95% CI: 5.6-7.7) and 11.0% (95% CI: 8.8-13.8) in patients with a low-, intermediate- and high-risk KRS, respectively, in the first 6-month period.

The low discriminatory capacity for VTE of the KRS in our cohort is also supported by the fact that 55.2% of patients who developed VTE had a baseline KRS <2, and therefore classified at low risk.

The failure of the KRS in identify patients at high VTE risk could be partially explained by differences between the HYPERCAN and the Khorana's cohort in which the score was developed, including the

study design and the different natural history of VTE across the various tumor types. Indeed, the HYPERCAN cohort is exclusively composed of 4 tumor sites, i.e., breast (14.7%), lung (39.4%), colon (34.2%), and gastric (12%), whereas the Khorana's cohort was composed mainly of breast (34.6%), lung (18.9%), ovarian (10%), colon (11.4%), gastric and pancreatic (1.7%) cancers, and lymphomas (12%), with a 10% of other tumor types. As can be observed, lung cancer is highly represented in our cohort (about 40%), and this tumor site is characterized by a low performance of KRS [17,19] that can affect its overall discrimination capacity. Accordingly, an individual patient data meta-analysis encouraged the use of the KRS to select high-risk patients with cancer types other than lung cancer for thromboprophylaxis [19]. Second, 20% of the patients of the Khorana's cohort had completed at least one chemotherapy cycle, whereas all our patients were naïve. In addition, only 38% of patients in the Khorana study population had metastatic cancer, compared with 100% in the HYPERCAN cohort, as for study design [29]. This difference may partly explain the higher incidence of VTE in our low-risk group according to the KRS. Finally, in the HYPERCAN cohort, a very low percentage of patients had a BMI $\geq$35 kg/m^2 (0.2% vs. 12% in the Khorana cohort), making this variable less relevant in the scoring system.

Interestingly, there was no improvement in risk stratification by the KRS when we applied a lower threshold of 2 points or more to identify high-risk patients; indeed, according to this dichotomous stratification, the cumulative incidence of VTE increased from 6.2% to 8.5% in the low-to-intermediate risk category, remaining approximatively stable at 11.8% in the high-risk category. Furthermore, the search for a more efficient cut-off value of the KRS in our cohort identified the 0 point as the best threshold for low- vs. high-risk classification, which however did not provide significant results.

As a second step, we tested the ability of the new-Vienna CATS score to significantly stratify our patients into different VTE risks. This score was developed in the CATS cohort (n = 1,423) and externally validated in the Multinational Cohort Study toIdentify Cancer Patients at High Risk of Venous Thromboembolism (MICA) study cohort (n = 832), characterized by an overall cumulative incidence of VTE at 6 months of 5.7% and 6.3%, respectively [25]. Since no cut-off values are provided for the new-Vienna CATS score, to assess differences in VTE risk between low- and high-risk patients, we decided to apply a predefined cut-off value of 5%, a risk level that is generally deemed high enough for considering thromboprophylaxis [34]. This risk level corresponds to a score of 60 points according to the new-Vienna CATS nomogram. Tested by ROC analysis, the 60 points were found to be a cut-off value with an acceptable specificity and sensitivity in our cohort. Based on this cut-off, the score provided a statistically significant SHR in the cohort of 924 patients evaluated for the KRS (7.3% vs. 11.7% SHR 1.7, $p = 0.023$) as well in the overall cohort (6.6 % vs. 12.2%, SHR 1.9, $p < 0.001$).

As previously discussed on the specificities of the Khorana's and the HYPERCAN cohorts, we must also make some considerations for the cohorts employed for the development and validation of the new-Vienna CATS nomogram. First, as observed for the Khorana's cohort, the CATS and MICA study populations were composed of patients with different tumor types compared to that of the HYPERCAN constituted of only 4 tumor types. In addition, about 30% of the patients of the CATS cohort had a history of cancer, whereas all our patients were newly diagnosed. Additionally, 70% of patients of the MICA cohort were receiving chemotherapy at enrollment, and a significant proportion of patients were diagnosed with esophageal cancer [25]. Finally, only 51% and 62% of patients in the CATS and MICA study populations, respectively, had metastatic cancer, as compared with 38% in the Khorana's cohort and 100% in the HYPERCAN cohort. However, despite these differences, the new-Vienna CATS score was able to significantly stratify our patients into 2 categories at different risk of developing VTE, also when applied to the overall cohort.

The fact that only metastatic cancer patients were enrolled in the HYPERCAN study may explain the differences observed in the cumulative incidences of VTE between the various cohorts, i.e., 2.2% 1-year VTE cumulative incidence in Khorana, and 5.7%, 6.3%, and 9.7% 6-month VTE cumulative incidence in CATS, MICA, and the HYPERCAN study populations, respectively. Indeed, we can infer that the higher the % of metastatic cancer included in the study cohort the higher the cumulative incidence of VTE. However, we should take into consideration that the cancer stage is not a variable included in any of the 2 RAMs we tested.

Perhaps the strength of the new-Vienna CATS score lies in the use of D-dimer, which was found to be significantly higher in patients who developed VTE than in those who remained VTE-free in our as well as previous studies [23,41]. D-dimer is a heterogeneous mixture of cross-linked fibrin degradation products and therefore represents an index of both coagulation and fibrinolytic activity. D-dimer testing in clinical practice is widely used to exclude thrombosis. Several assays employing diverse antibodies and different cut-off values are available, making a direct comparison of results impossible, and the identification of a common standard for data harmonization is still an unmet need [42]. In our study, we used the same assay used in the derivation cohort of the new-Vienna CATS score; we do not know whether the use of a different assay will provide the same positive results. Interestingly, an assay from a different manufacturer was utilized in the validation cohort (i.e., MICA) of the new-Vienna CATS score, with its prognostic performance maintained. It remains essential, however, that additional D-dimer assays need to be validated for use in this model.

The ability of the RAMs to predict cancer outcomes other than VTE is currently under active investigation. Although some clinical data suggested that a high KRS can predict death in patients with various malignancies [26–28], no data on this outcome are available for the new-Vienna CATS score. Therefore, in this analysis, we evaluated the performance of KRS and CATS scores in identifying cancer outpatients at a high risk of death and found that both scores showed a good performance in predicting OS. In particular, the cumulative incidence of mortality at 6 months was 9.9% vs. 26% (HR = 1.7, $p = 0.015$) by the KRS, and 7.4% vs. 23.9% (HR = 2.3, $p < 0.001$) by the new-Vienna CATS score, in the low-risk and high-risk categories, respectively.

That scores designed to predict VTE can also predict mortality may be related to the fact that some parameters of these scores are also prognostic for a worse outcome. For example, a high number of leukocytes (>11 × 10^9 cells/L), especially neutrophils, has been associated with early mortality [43], whereas anemia represents a poor prognostic factor for several malignancies including lung, pancreas, colon, breast, and ovarian cancer [44,45]. Similarly, elevated D-dimer levels in cancer have repeatedly been associated with a poorer prognosis [46,47]. Finally, it is as well recognized that cancer patients who develop VTE are at a higher risk of mortality [48].

The strength of our multicenter study is primarily based on the availability of a large prospective cohort with individual patient data, and objectively confirmed VTE events and mortality. Furthermore, the tumor sites included are among the most prevalent in Western countries, which contribute significantly to the global VTE burden.

In conclusion, the 2 scores showed a similar discrimination capability in our cohort, both with a valuable calibration plot. However, when we stratified by the pre-defined cut-off values, only the new-Vienna CATS score provided statistically significant SHR. In addition, our analysis revealed that KRS and the new-Vienna CATS score can effectively identify patients at the highest risk of 6-month mortality. The use of biomarkers of hemostasis for the development or improvement of existing RAMs may represent a promising direction to increase the prediction of risk of VTE and mortality.

APPENDICES

The members of the HYPERCAN Study (by centers, all in Italy) are the following:

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Fondazione ARTET Onlus Bergamo: Labianca Roberto.

Hospital San Filippo Neri, Rome: Gasparini Giampietro, Sarmiento Roberta, Gennaro Elisabetta. *Hospital San Giovanni, Rome*: Minelli Mauro.

Hospital Treviglio-Caravaggio, Treviglio: Barni Sandro, Petrelli Fausto, Ghilardi Mara.

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University of Milan Bicocca: Spinelli Daniele (Dept. Statistics), Marchetti Marina and Falanga Anna (Dept. Medicine and Surgery).

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AUTHOR CONTRIBUTIONS

C. Verzeroli: Formal analysis, Investigation, Writing - Original Draft, Visualization: C. Giaccherini Formal analysis, Investigation, Writing - Original Draft, Visualization: L. Russo Investigation, Visualization. S. Bolognini Investigation, Visualization: S. Gamba Investigation, Visualization: C.J. Tartari Investigation, Visualization: F. Schieppati Investigation, Visualization: C. Ticozzi Investigation, Visualization: A. Vignoli Investigation, Visualization; G. Masci Resources, Visualization; R. Sarmiento Resources, Visualization; D. Spinelli Formal analysis, Visualization: P. Malighetti Formal analysis, Visualization: C. Tondini Conceptualization, Resources, Visualization: F. Petrelli Conceptualization, Resources, Visualization: F. Giuliani Conceptualization, Resources, Visualization; A. D'Alessio Conceptualization, Resources, Visualization; G. Gasparini Conceptualization, Resources, Visualization; M. Minelli Conceptualization, Resources, Visualization: F. De Braud Conceptualization, Resources, Visualization: A. Santoro Conceptualization, Resources, Visualization: R. Labianca Conceptualization, Resources, Visualization; M. Marchetti Conceptualization, Validation, Writing - Review & Editing Supervision, Visualization; A. Falanga Conceptualization, Writing - Review & Editing, Supervision, Funding acquisition, Visualization, and Project administration. All authors read and approved the final version of the paper.

DECLARATION OF COMPETING INTERESTS

All authors declare that they have no potential conflicts of interest related to this research.

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SUPPLEMENTARY MATERIAL

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