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Original Article

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ABSTRACT

Background: In patients with cancer associated venous thromboembolism (CAT), risk factor-based scores for recurrence could drive clinical management. The aim of this study in patients with CAT was to develop and validate a risk score for recurrent venous thromboembolism (VTE) during anticoagulation: the Caravaggio score.
Methods: The Caravaggio score was developed in patients included in the Caravaggio trial and then externally validated in patients included in the TESEO registry. Potential predictors (univariate p-value ≤ 0.1) for recurrence were evaluated in a multivariable Cox regression model with death unrelated to VTE as competing event. Candidate predictors were identified and scored based on clinical relevance and β-coefficient. Patients were then categorized in three risk classes. The performance of the Caravaggio score was assessed by discrimination (c-statistics), sensitivity, specificity, positive and negative predictive value (NPV).
Results: Symptomatic VTE, ovarian and/or uterine cancer, pancreatic cancer, metastatic cancer, adenocarcinoma histological subtype, and pharmacological anticancer treatment were included in the score. In the derivation cohort, the incidence of recurrent VTE in the high, intermediate and low-risk groups was 11.6, 7.7 and 2.5 %, respectively. Incidences in the validation cohort were 8.0, 3.5 and 1.7 %, respectively. c-statistics in derivation and validation cohorts were 0.641 (95 % CI 0.584–0.698) and 0.606, (95 % CI 0.557–0.653), respectively. The NPV for low vs. intermediate/high-risk group was 98 % (95 % CI 95–99) in the derivation and 98 % (95 % CI 97–99) in the validation cohort.
Conclusions: The Caravaggio score is simple and able to stratify patients with CAT for the risk for VTE recurrence.

1. Introduction

Cancer associated venous thromboembolism (CAT) has a high risk of recurrence and treatment-emergent bleeding [1–4]. The identification of risk factors for venous thromboembolic (VTE) recurrence and bleeding would help clinicians to tailor the anticoagulant treatment in this setting. More specifically, the availability of risk factor-based scores for VTE recurrence and the resulting identification of different risk categories could optimize the benefit-risk ratios of anticoagulant treatment [5,6].

Several risk scores for recurrent VTE in patients with CAT have been developed including the Ottawa score, the modified Ottawa, the POMP-

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C, RIETE-VTE and one created by artificial intelligence [7–14]. Ottawa was also externally validated in the TROPIQUE and PREDICARE studies: c-statistics 0.60, 95 % confidence interval (CI) 0.55–0.65 and area under the receiver operating curve (AUC) of 0.53 (95 % CI 0.38–0.65), respectively [15,16]. Overall, these scores showed modest accuracy and low proportions of low risk patients to assess recurrent VTE. The most recently cancer-specific VTE recurrence score was developed with using artificial intelligence technology (natural language processing and machine learning) with promising results. This model identified type of VTE event, metastasis, adenocarcinoma, hemoglobin and serum creatinine levels, platelet and leukocyte counts, family history of VTE, and patients' age as predictors of VTE recurrence within 6 months of VTE diagnosis. The AUC for this model ranged from 0.66 to 0.69. However, this model has not been externally validated and cannot be recommended for use in clinical practice [17].

The aim of this study in patients with CAT was to develop and externally validate a clinical prediction score, the Caravaggio score, to assess the risk of VTE recurrence during anticoagulation.

2. Methods

2.1. Study population

The Caravaggio score was developed in the cohort of patients included in the Caravaggio trial [18,19] and was externally validated in the cohort of patients included in the TESEO registry [20,21].

Patients included in the Caravaggio trial and in the TESEO registry received anticoagulants for the treatment of CAT.

2.2. Model derivation

Caravaggio was a multinational, randomized, open-label, non-inferiority clinical trial with blinded assessment of the study outcomes aimed at assessing whether oral apixaban would be non-inferior to subcutaneous dalteparin for the prevention of recurrent VTE in patients with cancer. The primary outcome was objectively confirmed recurrent VTE, which included proximal deep vein thrombosis (DVT) of the lower limbs (symptomatic or incidental), symptomatic DVT of the upper limbs, pulmonary embolism (PE) (symptomatic, incidental, or fatal) occurring during the 6-month study period. The rationale, design and results of the Caravaggio study were previously reported [18,19].

2.3. Model validation

TESEO is an ongoing prospective, non-interventional, multicentric study including consecutive cancer patients with a diagnosis of thromboembolic event promoted by the Spanish Society of Medical Oncology (SEOM) [20,21]. For this analysis, patients with index proximal DVT or PE were included. Study outcomes were any objectively confirmed VTE recurrence (proximal DVT of the lower limbs, symptomatic DVT of the upper limbs, and PE) occurring within 6 months from index event.

2.4. Statistical analysis

For the derivation of the clinical prediction score, we referred to the post-hoc analysis of the Caravaggio study on risk factors for recurrent VTE [22]. A univariate analysis determined the strength of association between each potential predictor and VTE recurrence. All potential predictor variables (univariate p-value ≤ 0.1) were subsequently evaluated in a multivariable Cox regression model with death unrelated to the study outcome as a competing event. Data were presented as sub-distribution hazard ratios (sHR) and a p-value of < 0.05 was considered statistically significant. Candidate predictors were finally identified and scored by the study Steering Committee based on clinical relevance and results of statistical analyses (β-coefficient). The final model was set to identify three risk categories: high (≥6 points), intermediate (3–5 points) and low (≤2 points) risk of 6-month VTE recurrence. The final model (Caravaggio score) was chosen according to the best performance assessed by the following parameters: discrimination (c-statistic), sensitivity, specificity, positive and negative predictive value, low- and intermediate/high-risk patient distribution. In the multivariable analysis, no handling of missing value was planned, in case of missing values, patients were excluded from the analysis.

The final model was tested for i) internal validation through bootstrapping with 1000 iterations, and ii) calibration through calibration curve. The receiver operating characteristic (ROC) curve was used to illustrate the performance of the Caravaggio score in predicting recurrent VTE, and the corresponding AUC at 95 % CI was used to quantify its predictive value.

Once the model for recurrent VTE had been developed, the external validation was performed in patients included in the TESEO registry. In this population, the performance of the Caravaggio score was assessed by the following parameters: discrimination (c-statistics), sensitivity, specificity, positive and negative predictive value, low and intermediate/high risk patient distribution. The ROC curve and the corresponding AUC with 95 % CI were used to illustrate and quantify the performance of the Caravaggio score in predicting recurrent VTE. Calibration was assessed through a calibration plot (bootstrapping with 2000 replicates was applied). Data were reported according to the Tripod statement [23].

All data were analyzed with the use of SAS software, version 9.4 (SAS Institute).

3. Results

Overall, 1155 and 3506 patients with CAT were included in the derivation and validation cohorts, respectively. Baseline characteristics of the two cohorts were similar in terms of demographic and clinical features, type of VTE event and cancer sites, as shown in Table 1. The rate of anticancer treatment with platinum/fluoropyrimidine-based chemotherapy was higher in the Caravaggio cohort than in the TESEO cohort. At 6 months of follow-up, 78 (6.8 %) and 121 (3.5 %) recurrent VTE events occurred in the derivation and validation cohorts, respectively.

3.1. Model derivation

Symptomatic VTE, ovarian and/or uterine cancer, pancreatic cancer, metastatic cancer, adenocarcinoma histotype, and pharmacological anticancer treatment (platinum/fluoropyrimidine based chemotherapy) were independent predictors of recurrent VTE and were included in the Caravaggio score. Data from the univariable analysis and regression coefficients are reported in the supplementary material Table S1 and Table S2. Symptomatic VTE and metastatic cancer were assigned 2 points based on β-coefficient and clinical relevance, respectively. All other variables (ovarian and/or uterine cancer, pancreatic cancer, adenocarcinoma histotype, platinum/fluoropyrimidine based regimens) were assigned a score of 1. Table 2 reports the results from the multivariable analysis obtained with the predictors included in the Caravaggio score.

The incidence of VTE recurrence was shown to increase as the Caravaggio score point raises (Table 3).

The c-statistic of the Caravaggio score to predict recurrent VTE was 0.641, 95 % CI 0.584–0.698 (Fig. 1A, Table 4). The internal validation confirmed the results of the main analysis with a c-statistics of 0.632 (95 % CI 0.630–0.634). The calibration plot is shown in Figure S1A.

The distribution of the population according to the three risk categories is shown in Table 4. Overall, 12.7 %, 59.6 % and 27.7 % of patients were categorized as high, intermediate and low-risk. The incidence of recurrent VTE was 11.6 %, 7.7 % and 2.5 % in the high, intermediate and low-risk categories, respectively. The overall performance of the Caravaggio score was good at identifying patients with a

Table 1
Demographic and clinical characteristics of the patients included in CARAVAGGIO study (Derivation Cohort) and in TESEO registry (Validation Cohort).

Variable	Caravaggio, derivation cohort ($n = 1155$ patients)	TESEO, validation cohort ($n = 3506$ patients)
Age (years), mean±SD	66.8 ± 10.7	65.4 ± 11.5
Male gender, n %	568 (49.2)	1777 (50.7)
Weight (kg), mean±SD	75.9 ± 17.1	71.6 ± 15.4
Platelet count <100,000/mm3, n (%)	37 (3.2)	234 (6.7)
Creatinine clearance≤ 50 ml/min, n (%)	112 (9.7)	347 (9.9)
History of VTE, n (%)	106 (9.2)	268 (7.6)
Previous bleeding, n (%)	15 (1.3)	151 (4.3)
ECOG performance status ≥1, n (%)	801 (69.4)	2761 (78.8)
Qualifying diagnosis of venous thromboembolism		
Diagnosis of index DVT, n (%)	517 (44.8)	1578 (45.0)
Diagnosis of index PE, n (%)	638 (55.2)	1567 (44.7)
Diagnosis of index PE+DVT, n (%)	93 (8.1)	361 (10.3)
Symptomatic PE or DVT, n (%)	925 (80.0)	2623 (74.8)
Site of cancer		
Lung cancer, n (%)	200 (17.3)	781 (22.3)
Genitourinary cancer, n (%)	139 (12.0)	296 (8.4)
Ovarian and/or uterine cancer, n (%)	119 (10.3)	257 (7.3)
Colorectal cancer, n (%)	234 (20.2)	661 (18.9)
Upper gastrointestinal cancer, n (%)	54 (4.7)	216 (6.2)
Hepatobiliary cancer, n (%)	20 (1.7)	358 (10.2)
Pancreatic cancer, n (%)	67 (5.8)	98 (2.8)
Luminal GI (esophageal, stomach, colorectal) cancer, n (%)	272 (23.5)	877 (25.0)
Breast cancer, n (%)	155 (13.4)	365 (10.4)
Head and neck cancer, n (%)	22 (1.9)	72 (2.1)
Bone/Soft tissue cancer, n (%)	18 (1.6)	69 (2.0)
Skin- Melanoma cancer, n (%)	11 (0.9)	28 (0.8)
Hematological malignancy, n (%)	85 (7.4)	21 (0.6)
Type of cancer		
Adenocarcinoma histotype, n (%)	728 (63.0)	2388 (68.1)
Active cancer, n (%)	1124 (97.3)	2918 (83.2)
Metastatic cancer, n (%)	506 (43.8)	2488 (70.9)
Anticancer treatment		
Platinum/fluoropyrimidine based regimens, n %	831 (71.9)	1371 (39.1)
Anticoagulant treatment		
Direct oral anticoagulants, n (%)	576 (49.9)	127 (3.6)
Other anticoagulant therapy, n (%)	579 (50.1)	3285 (93.7)
No anticoagulants*, n (%)	–	93 (2.7)
Not available, n (%)	–	1 (0.0)

DVT=deep vein thrombosis; ECOG= Eastern Cooperative Oncology Group; PE=pulmonary embolism; SD=standard deviation; VTE=venous thromboembolism.
* palliative care or contraindication.

low risk of recurrence, the negative predictive value for low vs. intermediate/high-risk categories was 98 % (Table 4).

3.2. Model validation

The analysis conducted in CAT patients included in the TESEO cohort, confirmed the increase in the incidence of VTE recurrence as the Caravaggio score point raises (Table 3).

The discrimination of the Caravaggio score to predict recurrent VTE was identified by a c-statistic of 0.606 (95 % CI 0.557–0.653) in this cohort (Fig. 1B, Table 4). The calibration plot is reported in Figure S1B.

Overall, 7.1, 71.6 and 21.3 % of patients were categorized as high, intermediate and low-risk (Table 4). The incidence of recurrent VTE was 8.0, 3.5 and 1.7 % in the three risk groups, respectively. The negative predictive value was confirmed to be 98 % (95 % CI) (Table 4).

The incidence of recurrent VTE over time according to Caravaggio score in the validation cohort is shown in Fig. 2.

The risk of recurrent VTE is 2.76 times higher in patients categorized as high-risk (sHR 2.76, 95 % CI 1.57–4.85) and 1.32 times higher in those categorized as intermediate-risk (sHR 1.32, 95 % CI 0.87–2.01) compared with patients in the low-risk category.

Table 2
Multivariable Cox regression model for recurrent VTE in the derivation cohort.

Variable	Parameter Estimates	Adjusted sHR (95 % CI)	Score point°
Symptomatic VTE	0.60221	1.826 (0.949–3.516)	2
Ovarian and/or uterine cancer	0.51433	1.673 (0.869–3.220)	1
Pancreatic cancer	0.52287	1.687 (0.779–3.655)	1
Metastatic cancer	0.42159	1.524 (0.968–2.400)	2
Adenocarcinoma histotype	0.37778	1.459 (0.853–2.494)	1
Platinum/fluoropyrimidine based regimens	0.33543	1.399 (0.870–2.249)	1

Analysis based on multivariate Cox regression model with competing risk of death unrelated to clinical outcome. CI=confidence interval; sHR=sub-distribution hazard ratio.
° Score points assigned based on clinical relevance and β-coefficient.

Table 3
Incidence of recurrent VTE according to Caravaggio score in the derivation and validation cohorts.

Caravaggio score	Patients, n	VTE recurrence, n	VTE recurrence, %
Derivation cohort: CARAVAGGIO study			
0	26	0	0
1	57	1	1.8
2	237	7	2.9
3	252	14	5.6
4	216	19	8.8
5	220	20	9.1
6	117	15	12.8
7	30	2	6.7
Validation cohort: TESEO registry			
0	52	1	1.9
1	187	1	0.5
2	506	11	2.2
3	920	26	2.8
4	1035	42	4.1
5	556	20	3.6
6	205	18	8.8
7	45	2	4.4

VTE= venous thromboembolism.

4. Discussion

Our study reports on the derivation and validation of a new completely clinical score for the prediction of recurrent VTE in patients with CAT receiving anticoagulant treatment. In the derivation cohort, six variables were identified as predictors of recurrent VTE in patients with CAT on anticoagulant treatment and were embedded in a model that identified patients with low, intermediate and high-risk for VTE recurrence. The risks of recurrent VTE increased in patients in the higher risk categories. The Caravaggio score identifies more than one-fifth of CAT patients as having a low risk for recurrent VTE during the first 6 months of anticoagulant therapy (2.5 % in the derivation and 1.7 % in the validation cohorts, respectively). The negative predictive value for low vs. intermediate/high risk categories was 98 % in both the

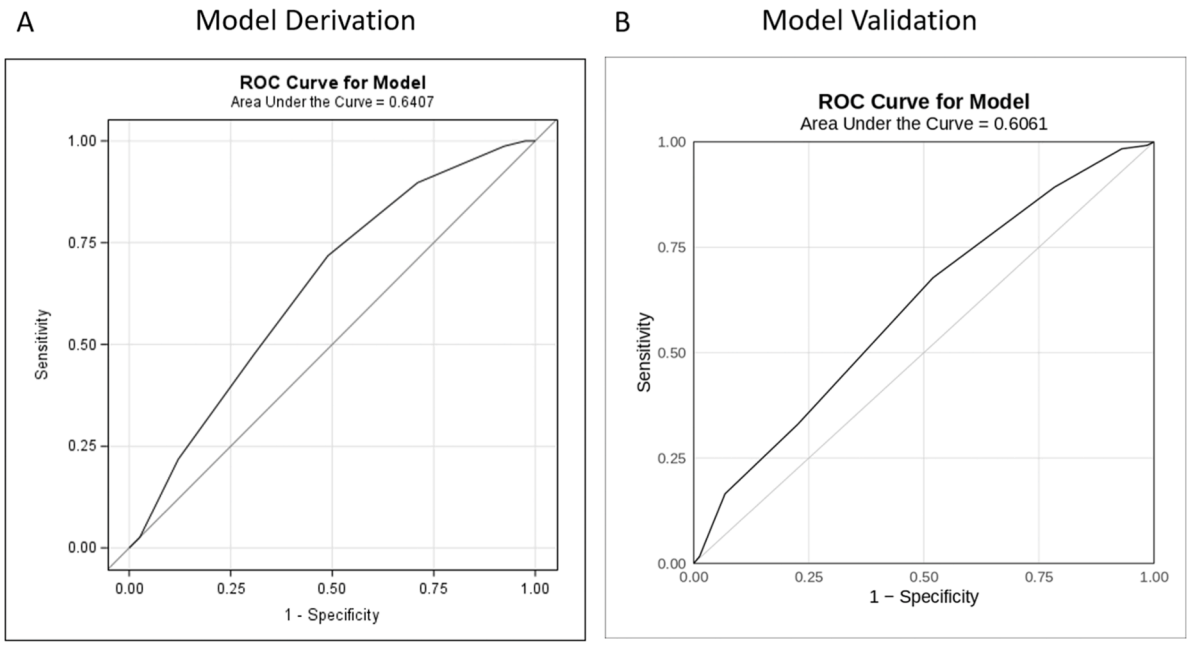

Fig. 1. ROC curve of the Caravaggio score for recurrent VTE in the derivation (A) and validation (B) cohorts.

Table 4
Performance of the Caravaggio score for recurrent VTE in the derivation and validation cohorts.

c-statistics (95 % CI)	Cut-off value	Risk group n (%)	Recurrent VTE according to risk group n (%)	Cut-off value	Recurrent VTE according to risk group n (%)	SE (95 % CI)	SP (95 % CI)	PPV (95 % CI)	NPV (95 % CI)
Derivation cohort[°]									
0.641 (0.584–0.698)	6–7	147 (12.7)	17 (11.6)	3–7	70 (8.4)	0.897 (0.811–0.947)	0.290 (0.263–0.318)	0.084 (0.067–0.105)	0.975 (0.952–0.987)
	3–5	688 (59.6)	53 (7.7)						
	0–2	320 (27.7)	8 (2.5)	0–2	8 (2.5)				
Validation cohort[#]									
0.606 (0.557–0.653)	6–7	250 (7.1)	20 (8.0)	3–7	108 (3.9)	0.893 (0.825–0.936)	0.216 (0.203–0.230)	0.039 (0.033–0.047)	0.983 (0.970–0.990)
	3–5	2511 (71.6)	88 (3.5)						
	0–2	745 (21.3)	13 (1.7)	0–2	13 (1.7)				

Percentages of events were calculated on total number of patients in each risk category group.
CI=confidence interval; VTE= venous thromboembolism; SE = Sensitivity; SP = Specificity; PPV = Positive Predictive Value; NPV = Negative Predictive Value.
[°] Percentages of patients in each risk category group were calculated on total number of patients in the modified Intent-To-Treat population of the Caravaggio study ($N = 1155$).
[#] Percentages of patients in each risk category group were calculated on total number of patients with cancer associated VTE in the population of TESEO registry ($N = 3506$).

derivation and validation cohorts.

The Caravaggio score has been designed to be practical and easy to apply. The choice of the variables was based on statistical analysis and clinical relevance. Unlike the other scores available for CAT patients as the Ottawa and modified Ottawa score, no negative points were assigned. Among variables associated with cancer site, the pancreatic and ovarian and/or uterine cancers were included in the Caravaggio score while the Ottawa score included lung and breast cancer sites (this last with a negative point). Furthermore, cancer severity was assessed with the inclusion of metastatic disease in the Caravaggio score, while it was based on cancer stage in the Ottawa score with a negative score assigned for stage I/II. Indeed, the presence of a metastatic disease increases the risk of recurrent VTE up to three-times and the presence of both pancreatic and metastatic cancer up to six-times [24–26]. Among other variables, we found that symptomatic presentation was strongly associated with recurrent VTE in patients with CAT. A recently published meta-analysis including three RCTs found that among patients with cancer, incidental VTE was associated with a lower rate of VTE recurrence compared with symptomatic VTE RR 0.62 (95 % CI 0.44–0.87) [27].

The distribution of recurrent VTE according to the three risk classes was similar in the Caravaggio score and the modified Ottawa score. Both scores showed a high negative predictive value for low vs. intermediate/high risk categories, confirming that they are suitable for identifying cancer patients with low risk of VTE recurrence. The low risk of recurrent VTE in this patient population nearly reflects the risk for recurrence in patients with non-cancer related VTE [28,29]. The novelty of the Caravaggio score is that the current derivation and validation cohorts include patients treated with new anticancer and anticoagulant therapies.

The high rate of recurrent VTE despite anticoagulant treatment in the high-risk patients, both in the derivation and validation cohorts (8.4 and

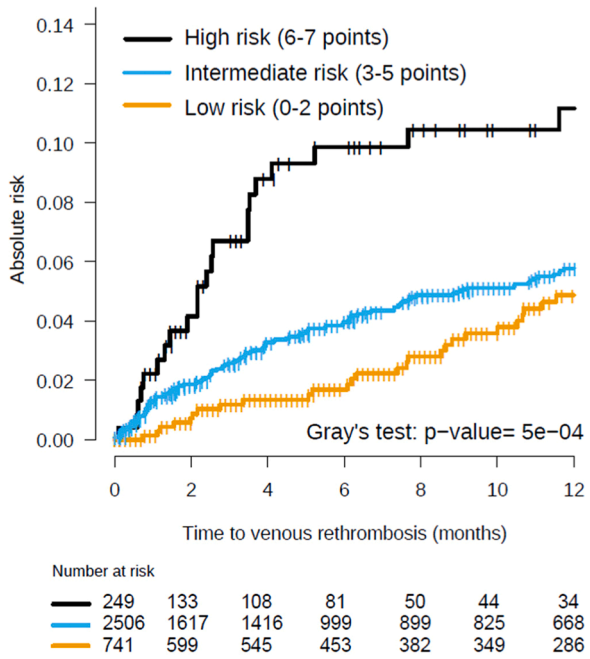

Fig. 2. Incidence of recurrent VTE over time according to the Caravaggio score (validation cohort).

3.9 %, respectively), indicates the need for urgent development of new therapeutic strategies in these patients. These high VTE recurrence rates are lower to those observed in the high risk category of Ottawa and modified Ottawa scores (18.6 % and 10.2 %, respectively) and similar to the high risk category of the RIETE-VTE score (5.1 %) [11,12]. The Caravaggio score can identify patients with high risk of recurrence and could be used to define the inclusion criteria of future studies evaluating novel treatment strategies in these patients.

Some limitations of this study should be considered. The open label design of the Caravaggio study may be considered a limitation; however, the adjudication of all study events was made by a blinded independent committee, which mitigates possible bias related to the open-label design. Patients with primary or metastatic brain cancer and acute leukemia were excluded from the Caravaggio study and, thus, the Caravaggio score cannot be applied to these patients. Patients were not equally distributed in the study cohorts across different cancer sites. This is a common finding in the "all-comers trials" where consecutive patients with cancer and VTE are included. This approach favors the inclusion of patients with cancer at sites where cancer is most common and with cancers that are more commonly associated with VTE. Indeed, the derivation and validation cohorts showed similar baseline characteristics and distribution of the sites of cancer. The rate of recurrent VTE was higher in the derivation than in the validation cohort. This maybe be due to some differences in the study populations as the rates of metastatic cancer, active cancer, and the use of platinum/fluoropyrimidine anticancer treatments. This could have led to the slight decrease in the AUC we found in the validation cohort. Furthermore, different anticoagulant treatment strategies were used in the derivation and validation cohorts. It is unlikely that anticoagulation influenced the role of predictors for recurrence. Finally, the discrimination performance of the Caravaggio score is not impressive considering the c-statistics (0.61–0.64). This might be due to the limitations listed above and, also by the point assignment. Indeed, all variables were assigned a score of 1 except the variable with the highest β-coefficient (symptomatic VTE) and a variable defined as clinically relevant by the Committee (metastatic cancer) who were assigned a score of 2. However, the c-statistics summarizes the discrimination of a model but does not communicate all the information ROC plot contains and lack direct clinical application. The more clinically relevant NPV was high in the Caravaggio score confirming its ability in selecting a population at low risk of recurrence with potential implication in the use of anticoagulant management.

Strengths of our study include its comprehensiveness and the large number of patients included in both the derivation and in the validation cohorts. Furthermore, the Caravaggio score was derived and validated in current cohorts of CAT patients where new anti-cancer and anticoagulant treatments (i.e. direct oral anticoagulants) were used, as also reported in previous publications [21,30].

In conclusion, the Caravaggio score is simple to perform as it is based on information available in every cancer patient. This score is able to stratify patients with CAT for the 6-month risk for VTE recurrence during anticoagulation.

Authorship contributions

MCV, AJMM, MG, CB, ACB, and GA study concept and design, major role in the acquisition of data, analysis or interpretation of data, drafting and revision of the manuscript for critically for important intellectual content, final approval of the version to be submitted.

PJF, MPMDP, FD, MVH, ATC, and RB major role in the acquisition of data, analysis or interpretation of data, drafting and revision of the manuscript for critically for important intellectual content, final approval of the version to be submitted.

Declaration of competing interest

MCV, no disclosures.

AJMM, consultant or advisory role for GSK, Pfizer, BMS-Celgene, Sanofi, Astra-Zeneca, MSD, Lilly, Servier, Roche, Taiho, Leo Pharma; research funding for Leo Pharma, Sanofi, Celgene; speakers' bureau for Rovi, Menarini, Stada, Medscape; patents, royalties, other intellectual property include risk assessment model in venous thromboembolism in cancer patients, liquid biopsy developed with laser technology.

MG, no disclosures.

PJF, consultant, advisory or speaker role for Astellas, AstraZeneca, Bristol-Myers Squibb (BMS), Esteve, Merck Sharp & Dohme (MSD), Novartis, Nutricia, Pfizer, Rovi, Takeda, Viatris.

CB, reports lecture fees and consultancies from Bayer, Bristol Myers Squibb, Pfizer, and Daiichi Sankyo.

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FD, reports lecture fees from Bayer, Bristol Myers Squibb, Pfizer, and Daiichi Sankyo.

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ACB, consultant or advisory role for Astellas; research funding for Leo Pharma, Sanofi; travel grants Amgen.

GA, has received honoraria (until December 2023) for lecture and advisory board contribution from BMS, Pfizer and Anthos Therapeutics.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2025.04.016.

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