

Development of a Clinical Prediction Rule for Risk Stratification of Recurrent Venous Thromboembolism in Patients With Cancer-Associated Venous Thromboembolism

Martha L. Louzada, MD, MSc; Marc Carrier, MD, MSc; Alejandro Lazo-Langner, MD, MSc; Vi Dao, MD; Michael J. Kovacs, MD; Timothy O. Ramsay, PhD; Marc A. Rodger, MD, MSc; Jerry Zhang, BSc; Agnes Y.Y. Lee, MD, MSc; Guy Meyer, MD; Philip S. Wells, MD, MSc

Background—Long-term low-molecular-weight heparin (LMWH) is the current standard for treatment of venous thromboembolism (VTE) in cancer patients. Whether treatment strategies should vary according to individual risk of VTE recurrence remains unknown. We performed a retrospective cohort study and a validation study in patients with cancer-associated VTE to derive a clinical prediction rule that stratifies VTE recurrence risk.

Methods and Results—The cohort study of 543 patients determined the model with the best classification performance included 4 independent predictors (sex, primary tumor site, stage, and prior VTE) with 100% sensitivity, a wide separation of recurrence rates, 98.1% negative predictive value, and a negative likelihood ratio of 0.16. In this model, the score sum ranged between -3 and 3 score points. Patients with a score ≤ 0 had low risk ($\leq 4.5\%$) for recurrence and patients with a score > 1 had a high risk ($\geq 19\%$) for VTE recurrence. Subsequently, we applied and validated the rule in an independent set of 819 patients from 2 randomized, controlled trials comparing low-molecular-weight heparin to coumarin treatment in cancer patients.

Conclusions—By identifying VTE recurrence risk in cancer patients with VTE, we may be able to tailor treatment, improving clinical outcomes while minimizing costs. (*Circulation*. 2012;126:448-454.)

Key Words: cancer ■ clinical prediction rule ■ venous thromboembolism ■ recurrence

For many years, management of venous thromboembolism (VTE) in cancer patients was similar to that for noncancer patients, that is, initial therapy with low-molecular-weight heparin (LMWH) or unfractionated heparin followed by vitamin K antagonists (VKAs) for at least 3 months.¹⁻⁴ However, in the early 2000s, Prandoni et al² demonstrated a significant increase in VTE recurrence risk in patients with malignancy compared with noncancer patients, with a 1-year cumulative incidence of recurrent VTE of 20.7% for cancer patients and 6.8% for noncancer patients (hazard ratio, 3.2; 95% confidence interval [CI], 1.9-5.4). Therefore, studies were developed that aimed to target a better treatment strategy for this population.⁵⁻⁸ These data were summarized in a systematic review of randomized, controlled trials (RCTs) that compared VKA versus LMWH for 3 to 6 months to treat cancer-associated venous thrombosis. The study demonstrated a VTE recurrence rate of 13% in patients treated with VKA and 7% in patients treated with LMWH, with

similar major bleeding rates of $\approx 5\%$.⁹ Therefore, the current standard of care for patients with cancer-associated VTE is long-term LMWH.¹⁰⁻¹²

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Nevertheless, the association between VTE recurrence risk and treatment management according to malignancy characteristics is largely unknown. A better understanding of the different malignancy characteristics that may influence the risk of VTE recurrence is needed, so that the practitioner may offer a better tailored treatment approach for the patient with cancer-associated VTE without exposing the patient to an unnecessary risk of bleeding and to the high psychological and financial cost of prolonged use of LMWH. We recently reported a systematic review that suggested that patients of younger age (< 65 years old) or with metastatic malignancy or lung malignancies sustain the greatest risk for recurrent

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From the Department of Medicine, Division of Hematology, London Health and Sciences Centre, University of Western Ontario, London, ON, Canada (M.L.L., A.L.-L., M.J.K.); Department of Medicine, Division of Hematology, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada (M.C., J.Z., T.O.R., M.A.R., P.S.W.); Department of Medicine, Division of Hematology, University of Manitoba, Winnipeg, MB, Canada (V.D.); Department of Medicine, Division of Hematology, University of British Columbia, Vancouver, BC, Canada (A.Y.Y.L.); and Division of Respiratory and Intensive Care Medicine, Hôpital Européen Georges Pompidou, Paris, France (G.M.).

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Correspondence to Martha de Lacerda Louzada, Department of Medicine, Division of Hematology, University of Western Ontario, 800-E3637 Commissioners Rd E, London, ON, Canada, N6A 5W9. E-mail martha.louzada@lhsc.on.ca

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VTE during the anticoagulation period, whereas patients with breast or hematologic malignancies have the lowest risk.¹³ These data suggest the potential for the development of a clinical prediction rule for stratification of a patient's risk for the development of a recurrent VTE during the anticoagulation period. Clinical prediction rules are appealing because they offer several potential benefits for practitioners, patients, and the healthcare system, such as a reduction in clinical uncertainty at the bedside and improvement of quality of care for patients. We report the derivation of a clinical prediction rule to stratify VTE recurrence risk in patients with cancer-associated thrombosis according to malignancy or other clinical characteristics. The preliminary rule was then run through a separate data set from 2 RCTs to validate and confirm its reproducibility.

Methods

Study Design and Selection of Participants

The derivation study was developed through a retrospective cohort, and the validation study was performed on patients included in 2 RCTs that compared VKA to LMWH for the treatment of cancer-associated thrombosis.^{7,8} The study was approved by the Ottawa Hospital Research Ethics Board.

In the derivation study, we conducted a chart review (electronic and hard copy) of patients with cancer and VTE who were diagnosed or followed up at the Thrombosis Unit of the Ottawa Hospital from January 2002 to December 2004 and from January 2007 to July 2008. These treatment periods were selected because it was expected that the vast majority of patients would have been treated with VKA for cancer-associated VTE in the first period, as was the standard of care at that time, and with LMWH, the current standard of care, in the second period. This would enable us to evaluate the effect of 2 different treatment strategies on recurrence risk.

All cancer patients in the region of 1.2 million people are treated at the Ottawa Hospital, and all thrombotic events in these patients are referred to the Thrombosis Assessment and Treatment Unit of the Ottawa Hospital. The end point for collection of data was either (1) that the patient developed a recurrent VTE during the first 6 months of anticoagulation; (2) the last time the patient was seen at the Ottawa Hospital, provided that the patient was still undergoing anticoagulation therapy; (3) when anticoagulation was terminated for any reason; or (4) death.

Because of the particularities intrinsic to patients with cancer-associated thrombosis, such as an inherent hypercoagulable state, vessel compression by tumor bulk, and invasive procedures, we designed the study to include all possibly significant VTE events. For this reason, we included data not only from adult patients (≥ 18 years of age) with active malignancy and objectively diagnosed index pulmonary embolism or proximal deep venous thrombosis (DVT) of the legs but also from patients with proximal DVT of the upper extremities or unusual site thrombosis. The VTE was considered cancer related if the patient had a diagnosis of cancer, other than basal cell or squamous cell carcinoma of the skin, within 6 months before or after VTE diagnosis, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer regardless of treatment.

Objectively proven DVT was defined as proximal DVT of the lower extremities confirmed by evidence of thrombus in the popliteal trifurcation or more proximal veins by compression ultrasound or contrast venography. Acute proximal DVT of the arms or neck was defined as objectively proven DVT confirmed by compression ultrasound or contrast venography with evidence of thrombus in the axillary vein or more proximal veins. At our institution, we do not image the calf veins; rather, we image from the calf trifurcation region proximally to the iliac veins. However, as per the recommended standard diagnostic strategy, if patients are likely to have DVT and have a negative initial ultrasound, the test is repeated 1

week later to detect proximal extension.¹⁴ Pulmonary embolism is defined by high probability on ventilation-perfusion lung scan (\dot{V}/\dot{Q} scan), the presence of filling defects in segmental or larger vessels, or multiple subsegmental filling defects on computed tomography pulmonary angiography.¹⁵⁻¹⁷ For the present study, single subsegmental filling defects were not considered to represent pulmonary embolism unless a concomitant DVT was diagnosed. Unusual site thrombosis was defined as a filling defect present at any site other than arms, legs, or lungs diagnosed through computed tomography, magnetic resonance imaging, or ultrasound of the abdomen, pelvis, or head (eg, cerebral sinus thrombosis, portal vein thrombosis, ovarian vein thrombosis), whether symptomatic or not.

Potential predictors were selected according to their well-reported relevance in influencing the risk of recurrent VTE in various populations.^{1,5-9,18-28} The potential predictors to be evaluated in the present study were sex, previous history of VTE, surgery (within 3 months of VTE recurrence), chemotherapy/hormone therapy (within 3 months of VTE recurrence), tumor stage, histology, primary tumor site, and D-dimer level at VTE recurrence.

Primary Outcome Measure

The primary outcome measure was VTE recurrence during the anticoagulation treatment period with objective tests as stated above, but for DVT recurrence, it required a new area of noncompressibility of a venous segment, an increase of the noncompressibility ≥ 4 mm, or a new constant intraluminal filling defect on venography, and for pulmonary embolism, new defects on computed tomography pulmonary angiography or \dot{V}/\dot{Q} lung scan. For unusual site thrombosis, confirmation required evidence of new thrombosis on the modality used for the original diagnosis, ie, computed tomography, magnetic resonance imaging, or ultrasound. Patients were routinely seen at 1 week, 1 month, and 3 and 6 months after diagnosis, and symptoms of recurrence were evaluated with objective imaging. Asymptomatic recurrences, if noted on follow-up investigations, were included.

Sample Size

The methodological criteria for the development of clinical prediction rules state that a minimum of 5 to 10 patients per predictor studied are required in the smallest outcome category.²⁹ We suspected that age, sex, stage of malignancy, histology, tumor site, and previous history of VTE would likely be relevant variables. To develop a clinical prediction model, we would need between 30 and 60 events (VTE recurrence cases) to include these 6 variables in the final logistic regression model, should they prove to be significant.

Derivation of Model

For the clinical prediction rule, we analyzed only the patients who had a recurrent VTE within the first 6 months of anticoagulation, because 6 months is the minimum standardized treatment approach for patients with cancer-associated VTE.^{7,11} SAS 9.2 was used for the analysis. Baseline characteristics of participants were analyzed by means of descriptive statistics. We used χ^2 or Fisher exact test for categorical variables, as appropriate.

A univariate analysis determined the strength of association between each potential predictor and VTE recurrence. All potential predictor variables ($P < 0.25$) were evaluated in a logistic regression analysis with backward variable selection (VTE recurrence as the dependent variable). The study steering committee (M.L.L., P.S.W., M.A.R., and T.O.R.) derived and reviewed 4 candidate models. The final model was chosen according to the best classification performance (risk of recurrence during anticoagulation, defined a priori [$< 7\%$]; lowest-risk excluded proportion; sensitivity, specificity, and negative predictive value; face validity; reasonable number of predictor variables; and ease of use). The final model was tested for internal validation through nonparametric bootstrapping by random sampling with replacement with 500 iterations. Estimates of the standard error and 95% CIs around the parameters' coefficients were compared with the original regression model.

To detect a possible temporal trend with respect to VTE recurrence risk, we included a variable that accounted for the 2 different

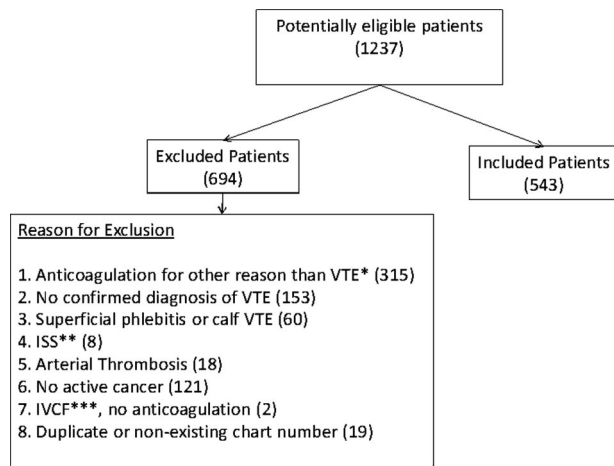


Figure 1. Flowchart of eligible patients in the derivation set. VTE indicates venous thromboembolism. *Perioperative management of patients with cancer taking anticoagulants because of atrial fibrillation or prosthetic heart valves. **Isolated subsegmental pulmonary embolism. ***Inferior vena cava filter.

time periods according to when patients were diagnosed and treated for cancer-associated VTE (from 2002–2004 and from 2007–2008). Hazard ratios for recurrent VTE were estimated for time period by multivariate Cox proportional hazard regression analysis in SPSS 20.0 software (IBM Corp).

External Validation of Model

Once the preliminary model was developed, the second step was to perform its external validation by applying the model in the pooled data set of 2 large RCTs that compared the use of VKA or LMWH in patients with cancer-associated VTE.^{7,8} These 2 data sets, however, differed from our retrospective study with respect to solid tumor classification. We classified our patients as TNM (tumor, nodes, and metastasis classification) stage I versus II+III+IV, whereas they classified their patients as TNM stage I+II versus III+IV, and the data they collected did not enable separation of stages I and II. Therefore, we had to adjust our derivation model to this minor difference and combine stages I and II, then III and IV. Our new model was then rerun and compared with the validation data set.

Results

Derivation Set

For the derivation study, there were 1237 potential patients, of whom 694 did not fulfill our inclusion criteria, which left 543 patients for inclusion in the present analysis (Figure 1). As described previously, our derivation set comprises 2 cohorts of patients diagnosed with cancer and VTE: From 2002 to 2004 and from 2007 to 2008. From 2002 to 2004, 142 patients were evaluated. Among them, 110 patients (77.5%) used VKA for long-term anticoagulation, and LMWH was the long-term therapy of choice in 32 patients (22.5%; $P=0.0001$). From 2007 to 2008, 401 patients were diagnosed and followed up at the Thrombosis Unit of the Ottawa Hospital. Among them, 89 (22.2%) used VKA for long-term anticoagulation, and 312 (77.8%) used LMWH ($P=0.0001$).

In total, the long-term anticoagulation of choice was VKA in 200 patients (36.8%) and LMWH in 343 (63.2%; $P=0.0001$). There were 240 males (44.2%). Mean age of participants was 63 years. There were 58 patients (10.7%) with hematologic malignancies and 485 (89.3%) with solid tumors. At VTE presenta-

Table 1. Baseline Characteristics of Derivation and Validation Study Samples

Predictor Variables	Derivation Study (n=543)	Validation Study (n=819)
Male/female, n (%)	240/303 (44/56)	392/427 (48/52)
Primary tumor site, n (%)		
Lung	96 (17.7)	106 (12.9)
Breast	85 (15.6)	139 (17.0)
Gastrointestinal	140 (25.8)	179 (21.9)
Other	164 (30.2)	309 (37.7)
Hematologic	58 (10.7)	86 (10.5)
Prior VTE, n (%)	46 (8.5)	96 (11.7)
TNM stage,* n (%)	I=61 (12.6)	I+II=277 (37.8)
	II=74 (15.3)	III+IV=526 (71.8)
	III=84 (17.3)	
	IV=237 (48.9)	

VTE indicates venous thromboembolism; TNM, tumor-nodes-metastasis staging system.

Values are n (%).

*TNM for solid tumors only: Derivation study (n=485) and validation study (n=733).

tion, 238 patients (43.8%) had distant metastasis. Adenocarcinoma was present in 306 (63.1%) of 485 patients with solid tumors. Details of baseline characteristics are shown in Table 1.

Fifty-five patients developed recurrent VTE within the first 6 months of anticoagulation. There were 19 (9.5%) recurrent events in patients taking VKA and 36 (10.5%) in patients taking LMWH (relative risk, 1.13; 95% CI, 0.743–1.711; $P=0.565$), which means there was a similar risk of recurrence irrespective of treatment strategy.

The univariate analysis suggested that sex, presence of lung cancer, breast cancer, histology, TNM stage I disease, history of prior VTE, and surgery were potentially relevant predictors to be further tested in the logistic regression model. The multivariate analysis suggested that only sex and primary tumor site were independent predictors of recurrence ($P<0.05$), but tumor stage and prior history of VTE were variables close to significance, so we tested them in our models. The model with the best classification performance was the model that included all 4 independent predictors (sex, primary tumor site, stage, and prior VTE.) with 100% sensitivity, the widest separation by recurrence rates, 98.1% negative predictive value, 48.1% low-risk excluded proportion, and a good negative likelihood ratio of 0.155. In this model, the score sum ranged between -3 and 3 score points. High-risk predictors received 1 point each (female=1, lung cancer=1, history of previous VTE=1). Low-risk predictors received negative points (breast cancer= -1 and TNM stage I= -2). Patients with a score ≤ 0 had low risk ($\leq 4.5\%$) for VTE recurrence. Patients with a score ≥ 1 had a high risk ($\geq 19\%$) for VTE recurrence (Table 2).

Because we combined the data of all patients regardless of type of anticoagulant used (VKA or LMWH) in the derivation model, we decided to run the model according to treatment strategy to evaluate whether this would have a significant impact on the risk of recurrence. Once again, there was a clear dichotomization of risk in both subgroups. In the

Table 2. Ottawa Score for Recurrent VTE Risk in Cancer-Associated Thrombosis

Variable	Regression Coefficient	Points
Female	0.59	1
Lung cancer	0.94	1
Breast cancer	-0.76	-1
TNM* stage I	-1.74	-2
Previous VTE	0.40	1
Clinical probability		
Low (≤ 0)	...	-3 to 0
High (≥ 1)	...	1 to 3

VTE indicates venous thromboembolism.

*TNM (tumor-nodes-metastasis staging system) for solid tumors only.

LMWH group, patients who scored ≤ 0 had low risk ($\leq 3.0\%$) for VTE recurrence. Patients with a score ≥ 1 had a high risk ($\geq 17.5\%$) for VTE recurrence. Patients using VKA who scored ≤ 0 had a low risk ($\leq 5.6\%$) for VTE recurrence. Patients with a score ≥ 1 had a high risk ($\geq 13.8\%$) for VTE recurrence. Cox regression analysis was used to evaluate whether treatment strategy (VKA or LMWH) or time of diagnosis had an impact on VTE recurrence. We found no significant statistical difference in recurrence risk in patients treated with either medication (adjusted hazard ratio, 1.380; 95% CI, 0.675–2.825; $P=0.378$) or in patients diagnosed and treated for VTE between 2002 and 2004 or between 2007 and 2008 (adjusted hazard ratio 1.696; 95% CI, 0.744–3.862; $P=0.209$; Figure 2).

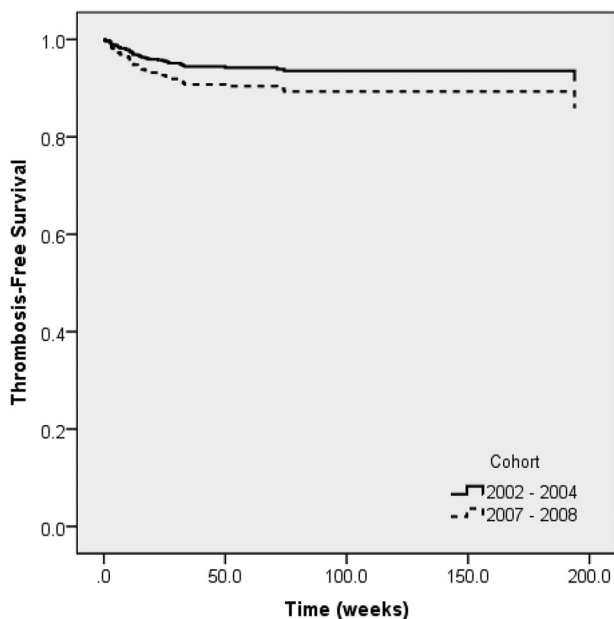


Figure 2. Cox proportional regression for evaluation of venous thromboembolism (VTE) recurrence risk in study sample (derivation model) according to temporal trend. Cohort 2002–2004 indicates patients diagnosed with cancer-associated VTE during this time period; cohort 2007–2008, patients diagnosed with cancer-associated VTE during this time period. Adjusted hazard ratio, 1.696; 95% confidence interval, 0.744–3.862; $P=0.209$.

External Validation Set

For the external validation, given the limitations of the data in the 2 randomized trials as described above, we had to reclassify tumor stage in our derivation set such that stages I and II were combined as a single variable and stages III and IV were combined as a single variable. We then reran our derivation model (before running the model in the validation data set). This changed the derivation model such that stage I+II was assigned a score of -1 (different from the -2 in our original model). This model was less discriminatory, which resulted in a prediction rule that gave a recurrence risk that was no longer clearly dichotomized but rather gave a low-, intermediate-, and high-risk group (Table 3).

This revised model was then applied to the 819 consecutive patients with cancer-associated VTE from the 2 multicenter RCTs (ClotCant group: CLOT trial [Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients With Cancer] and CANTHANOX trial [Secondary Prevention Trial of Venous Thrombosis with Enoxaparin] data set). In total, 86 patients (10.5%) had VTE recurrence in these trials. Patients with a score < 0 had a low risk (5.1%) for VTE recurrence, and this represented 19% of the patient population; patients with a score of zero had an intermediate risk (9.8%), representing 42% of patients; a score ≥ 1 , indicating high risk (15.8%), occurred in 38% of the population. Dichotomizing the results gave a recurrence risk of 7.5% in patients with a score ≤ 0 and a 15.8% recurrence risk if the score was > 0 (Table 3).

Discussion

In the present study, we were able to identify 4 independent predictors of VTE recurrence (sex, primary tumor site, tumor stage, and prior VTE) in the setting of cancer-associated thrombosis that could be combined into a model that clearly predicted a low and high risk of VTE recurrence in patients undergoing anticoagulant treatment for cancer-associated VTE. In our validation study, we were unable to fully validate the derivation model as it was originally developed because of data limitations in the validation set. However, the second similar model we developed, as a consequence of needing to combine TNM stage I and II malignancy as a single variable, was validated in the data from 2 RCTs. This model appears best suited to predict patients at low, intermediate, and high risk for recurrence. The validation data set suggests the robustness and reproducibility of the original model.

Our results are plausible and consistent with the literature. With regard to disease stage, observational studies that evaluated the incidence of a first VTE in patients with active malignancy found a 2- to 19-fold higher incidence among patients with distant metastasis than in patients with localized disease.^{19,26,28} Blom et al¹⁹ conducted a case-control study to evaluate the risk of a first VTE in >5000 patients with diverse types of malignancy; patients with metastasis had a significantly higher risk of VTE (odds ratio, 67.7; 95% CI, 9.4–486.6). Later, Blom et al¹⁸ prospectively evaluated 2149 patients with lung cancer and found an increased relative risk for a first VTE associated with malignancy of 1.9 (95% CI, 1.9–2.3) for patients with metastasis compared with patients

Table 3. Final Score in the Derivation and Validation Samples

Sum of Points	Derivation Study* (n=543)			Validation Study† (n=819)		
	Patients, n	VTE Recurrence, n	Frequency of VTE Recurrence, %	Patients, n	VTE Recurrence, n	Frequency of VTE Recurrence, %
−3	0	0	0	0	0	0
−2	33	0	0	0	0	0
−1	24	1	4.2	158	8	5.1
0	215	10	4.7	245	34	9.9
1	218	34	15.6	263	34	12.9
2	49	9	18.4	51	9	17.7
3	4	1	25.0	2	1	50.0

VTE indicates venous thromboembolism.

*Derivation set: Ottawa retrospective study.

†Validation set: ClotCant group (CLOT trial [Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients With Cancer] and CANTHANOX trial [Secondary Prevention Trial of Venous Thrombosis with Enoxaparin] data set).

VTE recurrence risk for patients in the derivation study with low (≤ 0) clinical probability was 4.5%; for those with high clinical probability (≥ 1), it was 19.7%. VTE recurrence risk for patients in the validation study with low (≤ -1) clinical probability was 5.1%; for those with intermediate (zero) clinical probability, it was 9.9%; and for those with high (≥ 1) clinical probability, it was 15.8%.

without metastasis. More recently, Chew et al²¹ suggested that patients with metastases had a 4- to 13-fold increase in their risk for VTE compared with patients who had localized disease.

Two large administrative database studies suggest that the most common malignancies associated with development of a first VTE are lung cancer, colorectal cancer, breast cancer, and lymphomas.^{25,27} Levitan et al²⁵ evaluated >7000 patients with cancer over a total cohort of 10 million hospitalized patients in the US Medicare database. The rate of a first VTE was not clearly reported, but the study stated that renal, gastrointestinal, brain, and ovarian cancer and lymphomas were the most frequent types of malignancies that predisposed to VTE compared with head/neck, bladder, and breast cancer, with relative risk of DVT/pulmonary embolism of 4.13 (95% CI, 3.82–4.45). Another large administrative database study evaluated 34 000 records of patients with various malignancies and suggested that the concomitant diagnosis of VTE and cancer is much more prevalent in patients with lung and gastrointestinal cancer (17% each) than in patients with breast (3.6%) or prostate (7%) cancer.²⁷ One retrospective cohort study reviewed the charts of 529 patients with cancer-associated DVT. They found similar results, with lymphomas presenting with the highest rates of a first VTE at 15%, followed by breast cancer (13%) and lung and gastrointestinal malignancies (11% each).²³ An accurate rate of VTE recurrence according to primary tumor site has not been established.

As for the scarce literature on VTE recurrence risk in the context of malignancy, the CLOT trial post hoc analysis suggested that lung cancer (hazard ratio, 3.51; 95% CI, 1.62–7.62) and metastasis (hazard ratio, 2.59; 95% CI, 1.29–5.60) were independent predictors of VTE recurrence in the context of cancer-associated VTE.³⁰ Conversely, breast cancer (hazard ratio, 0.59; 95% CI, 0.17–2.01) showed a trend toward being a low risk. Our systematic review also suggested that patients with cancer-associated thrombosis do indeed have varying VTE recurrence risk influenced by malignancy characteristics, with metastasis (relative risk, 1.36; 95% CI, 1.06–1.74; $P=0.01$) and

lung or gastrointestinal malignancies increasing the risk of recurrence and with patients with breast cancer and hematologic malignancies presenting with a lower risk.¹³

The present study has potential limitations. The first derived model could not be fully tested in the data from the randomized trials used for external validation, and the scoring system that groups stages I and II as a single variable appears to be less discriminatory than our original model, which suggests an advantage to classifying patients' tumor stage as TNM stage I versus stage II, III, and IV. Wasson et al²⁹ published the methodological standards for clinical prediction rules, and later, those standards were updated.²⁴ Wasson et al stated that the outcome to be predicted must be clearly defined and clinically important, and the assessment of the outcome must be blinded. Therefore, it is ideal for a prediction rule to be derived in a prospective study with blinded outcome assessment, which was not possible with a retrospective design. However, the clinical findings used as predictive variables were clearly defined and standardized, and their assessment was performed without knowledge of the outcome, which fulfills the Wasson criteria. In addition, we were able to demonstrate the reproducibility and accuracy of the clinical findings used as predictive variables and of the rule itself in a second independent set of patients.

Regarding other potential predictor variables not studied in the model, we elected not to include D-dimer testing because only 13% of patients had D-dimer levels assessed at both the first and recurrent episodes of VTE. Similarly, we were unable to evaluate the role of thrombocytosis or leukocytosis/leukopenia at recurrence. These markers are being studied in the setting of a first VTE in the context of malignancy.^{22,31–33} They are likely to be soft outcomes for evaluation of recurrence, because they most likely will reflect the impact of the anticancer treatment (chemotherapy/radiation therapy) and could act as confounders in the VTE recurrence setting. Treatment strategy was not a predictor of recurrence. In the present study, there was no difference in VTE recurrence rate according to treatment strategy (relative risk, 1.13; 95% CI, 0.743–1.711; $P=0.565$).

Furthermore, a subgroup analysis that applied the clinical prediction rule to patients who used long-term VKA or long-term LMWH demonstrated that our prediction tool worked accurately independent of treatment approach. Regardless, for a clinical prediction rule to be accurate and useful, it does not need to contain all possible independent predictors. Conversely, it has to be sensible and relevant, demonstrate face and content validity, be concise, and be easy to use in the intended clinical application. Most important, the included predictors must reliably reflect the outcome risk the rule is supposed to predict. Although we derived our clinical prediction rule with a retrospective data set, all recurrent events were accurately objectively diagnosed with clinical and imaging techniques, and data were collected prospectively.

In summary, regardless of the use of a 3-category score or a dichotomized score, our model appears to differentiate risk for recurrence and could be used in treatment trials attempting novel treatment strategies in high-risk patients, because LMWH alone does not appear to be sufficient. For low-risk patients, a case could be made for using the less costly typical LMWH followed by oral anticoagulants treatment regimen to evaluate whether oral anticoagulants can be as safe and effective as long-term LMWH. Patients with cancer-associated thrombosis clearly behave differently with respect to risk of recurrent VTE depending on malignancy and clinical characteristics. A prediction model that assigns a score of -2 for stage I cancer, -1 for breast cancer, and $+1$ for lung cancer, female sex, and previous VTE allows for prediction of low risk for recurrent VTE when the score totals ≤ 0 and high risk if the score is >0 . We hope we will be able to demonstrate in a future prospective trial that this rule is reproducible, generalizable, safe, and a useful tool for clinicians to help them improve care for patients with cancer-associated VTE.

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Disclosures

In the past 5 years, Dr Rodger has received honoraria for presentations for Pfizer, Boehringer Ingelheim, GTC Therapeutics, bioMerieux, and Leo Pharma. In the past 5 years, Dr Wells has received honoraria for presentations for Bayer, bioMerieux, Sanofi Aventis, and Boehringer Ingelheim. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Cancer patients who experience a venous thromboembolic event are at much higher risk of recurrent events while undergoing anticoagulation than any other patient group with similar events. As such, it can be argued that treatment is frequently ineffective, and new treatment strategies are warranted. However, given the heterogeneity of the cancer population, it is probable that not all cancer patients have this similar high risk. We have developed a prediction tool that enables us to identify a high-risk group with a risk of recurrence on the order of 20% and a low-risk group with a risk of recurrence on the order of 5%. This tool will allow us to identify patients in whom a closer vigilance is required and in whom new therapeutic strategies should be tested. The parameters used are very simple and include sex, primary tumor site and stage, and a history of prior venous thromboembolism. These are clinical parameters that are usually collected in all patients, thus ensuring the ease of use and applicability of this model.

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