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

Running title: Louzada et al.; A risk score for thrombosis recurrence in cancer

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Abstract:

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 (≤4.5%) for recurrence and patients with a score above 1 had a high risk (≥ 19%) for VTE recurrence. Subsequently, we applied and validated the rule in an independent set of 819 patients from 2 randomized controlled trials comparing LMWH 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.

Key words: cancer; clinical prediction rule; venous thromboembolism recurrence
Background

For many years management of venous thromboembolism (VTE) in cancer patients was similar to non-cancer patients. That is, initial therapy with low molecular weight heparin (LMWH) or unfractionated heparin followed by vitamin K antagonists (VKA) for at least 3 months. However, in the early 2000s Prandoni et al. demonstrated a significant increase in VTE recurrence risk in patients with malignancy compared to non-cancer patients, with a 1-year cumulative incidence of recurrent VTE of 20.7% for cancer patients and 6.8% for non-cancer patients (hazard ratio, 3.2; 95% CI 1.9-5.4). As such, studies were developed aiming to target a better treatment strategy for this population. These data were summarized in a systematic review of randomized controlled trials (RCT) that compared VKA versus low molecular weight heparin (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 treat with LMWH with similar major bleeding rates of approximately 5%. Therefore, the current standard of care for patients with cancer-associated VTE is long-term LMWH.

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 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 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 with younger age (less than 65 years old), or metastatic malignancy, or lung malignancies sustain the greatest risk for recurrent VTE during the anticoagulation period whereas patients with breast or hematological malignancies have the
lowest risk. These data suggest the potential for the development of a clinical prediction rule (CPR) for stratification of patient’s risk for the development of a recurrent VTE during the anticoagulation period. CPRs are appealing because they offer several potential benefits for practitioners, patients and the Health Care System such as, reduction in the 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 dataset from 2 RCTs to validate and confirm its reproducibility.

Materials/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 randomized controlled trials that compared VKA to LMWH for the treatment of cancer-associated thrombosis. The study was approved by the Ottawa Hospital Research Ethics Board.

In the derivation study we conducted a chart review (electronic and hardcopy) from patients with cancer and VTE who were diagnosed and/or followed 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 in the second period, the current standard of care. This would enable us to evaluate the effect of two different treatment strategies on recurrence risk.
All cancer patients in the region of 1.2 million 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) The patient developed a recurrent VTE during the first 6 months of anticoagulation; 2) The last time patient was seen at the Ottawa Hospital provided that he/she was still on anticoagulation; 3) When anticoagulation was terminated for any reason; or 4) death.

Due to the particularities intrinsic to patients with cancer-associated thrombosis such as inherent hypercoagulable state, vessel compression by tumour bulk and invasive procedures to name a few; we designed the study to include all possibly significant venous thromboembolic events. For this reason, we included data from adult patients (18 years of age or older) with active malignancy and objectively diagnosed index pulmonary embolism (PE) and/or proximal deep venous thrombosis (DVT) of the legs, but also patients with proximal DVT of the upper extremities or unusual site thrombosis. The VTE is 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 is 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 and/or neck is defined as objectively proven DVT confirmed by compression ultrasound or contrast venography with evidence of thrombus in the axillary vein or more proximal veins. In our institution we do not image the calf veins, rather from the calf trifurcation region proximally to the iliac veins. However, as per the recommended standard diagnostic strategy if patients were DVT likely with
a negative initial ultrasound the test is repeated one week later to detect proximal extension\textsuperscript{14}.

PE is defined by high probability on ventilation-perfusion lung scan (V/Q scan) or by the presence of filling defects in segmental or larger vessels, or multiple subsegmental filling defects on Computerized Tomography Pulmonary angiography (CTPA)\textsuperscript{15-17}. For this study, single subsegmental filling defects were not considered to represent PE, unless a concomitant DVT was diagnosed. Unusual site thrombosis is defined as a filling defect present at any site other than arms, legs or lungs diagnosed through Computerized tomography, or Magnetic resonance imaging (MRI) or Ultrasound of the abdomen, pelvis or head (e.g. cerebral sinus thrombosis; portal vein thrombosis, ovarian vein thrombosis) symptomatic or not.

Potential predictors were selected according to their well reported relevance influencing risk of recurrent VTE in various populations\textsuperscript{1;5-9;18-28}. The potential predictors to be evaluated in this study are: sex, previous history of VTE, surgery (within 3 months of VTE recurrence), chemo/hormonetherapy (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 above but for DVT recurrence it required a new area of noncompressibility of a venous segment or an increase of the noncompressibility $\geq 4$mm or a new constant intraluminal filling defect on venography, and for PE, new defects on CTPA or V/Q lung scan. For unusual site thrombosis confirmation required evidence of new thrombosis on the modality used for the original diagnosis ie CT, MRI or ultrasound. Patients were routinely seen at one week, one month, three and six months post 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 states that a minimum of 5 to 10 patients per predictor studied are required in the smallest outcome category. 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 to 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 analysed only the patients who had a recurrent VTE within the first 6 months of anticoagulation since 6 months is the minimum standardized treatment approach for patients with cancer-associated VTE. SAS 9.2® was used for the analysis. Baseline characteristics of participants were analyzed by means of descriptive statistics. We used chi-square or Fisher’s 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 (ML, PW, MR and TR) 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 (less than 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 non-parametric bootstrapping using random sampling with replacement with 500
iterations. Estimates of the standard error and 95% confidence intervals 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 accounting for the 2 different time periods according to when patients were diagnosed and treated for cancer-associated VTE: from 2002 to 2004 and from 2007 to 2008. Hazard ratios for recurrent VTE were estimated for time period using 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 dataset of 2 large RCTs that compared the use of VKA or LMWH in patients with cancer-associated VTE. These 2 datasets, 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 stage I and II. Therefore, we had to adjust our derivation model to this minor difference and combine stage I and II, then III and IV. Our new model was then, rerun and compared to the validation data set.

**Results**

**The Derivation Set**

For the derivation study there were 1237 potential patients, of whom 694 did not fulfill our inclusion criteria, leaving 543 patients for inclusion in this analysis (*Figure 1*). As previously described, 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, one hundred and forty-two patients were evaluated. Among them 110 (77.5%) patients 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 at the Thrombosis Unit of the Ottawa Hospital. Among them 89 (22.4%) patients 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 (36.6%) patients and LMWH in 343 (63.3%) patients \( (p = 0.0001) \). There were 240 (44.2%) males. Mean age of participants was 63 years. There were 58 (10.7%) patients with hematological malignancies and 485 (89.3%) patients with solid tumors. At VTE presentation, 238 (43.8%) patients had distant metastasis. Adenocarcinoma was present in 306 of 485 (63.1%) 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 on VKA and 36 (10.5%) in patients on LMWH \([\text{RR} = 1.13 \ (95\% \text{CI}, 0.743 - 1.711; \ p = 0.565)\] ), meaning 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 significant 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 (≤4.5%) for VTE recurrence. Patients with a score equal or above 1 had a high risk (≥ 19%) for VTE recurrence (Table 2).

Since 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 it would significantly impact on the risk of recurrence. Once again, there was a clear dichotomization of risk in both subgroups. In the LMWH group, patients that scored ≤ 0 had low risk (≤ 3.0%) for VTE recurrence. Patients with a score equal or above 1 had a high risk (≥ 17.5%) for VTE recurrence. Patients using VKA that scored ≤ 0 had low risk (≤ 5.6%) for VTE recurrence. Patients with a score equal or above 1 had a high risk (≥ 13.8%) for VTE recurrence. Cox regression analysis was used to evaluate whether treatment strategy (VKA or LMWH) or time of diagnosis would 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 to 2004 or between 2007 to 2008 (Adjusted Hazard ratio 1.696; 95%CI (0.744, 3.862); p=0.209). (Figure 2).

The External Validation Set

For the external validation, given the limitations of the data in the two randomized trials as described above, we had to reclassify tumor stage in our derivation set such that stage I and II
were combined as a single variable and III and IV were combined as a single variable. We then, reran our derivation model (before running the model in the validation dataset). 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 resulting in a prediction rule which gave a recurrence risk that was no longer clearly dichotomized, rather gave a low, intermediate, and high risk groups (Table 3).

This revised model was then applied to the 819 consecutive patients with cancer-associated VTE from the two multicentre randomized controlled trials (ClotCant group). 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 a intermediate risk (9.8%) and this represented 42% of patients; a score ≥ 1 were high risk (15.8%), occurring 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 this 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 can be combined into a model that clearly predicts a low and high risk of VTE recurrence in patients on anticoagulant treatment for cancer-associated VTE. In our validation study we were unable to fully validate the derivation model as it was originally developed, due to 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
randomized controlled trials. This model appears best suited to predict patients at low, intermediate and high risk for recurrence. The validation dataset suggests robustness and reproducibility of the original model.

Our results are plausible and consistent with the literature. In regards 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. Blom et al. conducted a case-control study to evaluate the risk of a first VTE in more than 5,000 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 al. 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 to patients without metastasis. More recently, Chew et al. suggested that patients with metastases had a 4-to-13 fold increase in their risk for VTE compared with patients having 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. Levitan et al. evaluated over 7 thousand patients with cancer over a total cohort of 10 million hospitalized patients of the USA Medicare database. The rate of a first VTE was not clearly reported but the study stated that renal cancer, GI, brain and ovary cancer as well as lymphomas were the most frequent types of malignancies that predisposed to VTE compared to head/neck, bladder and breast with relative risk of DVT/PE of 4.13 (95%CI; 3.82 – 4.45).

Another large administrative database study evaluated 34,000 records of patients with various malignancies and it 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 cancer (7%) \(^27\). 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%), lung and gastrointestinal malignancies (11% each) \(^23\). An accurate rate of VTE recurrence according to primary tumor site is not established.

As for the scarce literature in VTE recurrence risk in the context of malignancy, the CLOT trial post-hoc analysis suggested that lung cancer [HR = 3.51 (1.62 - 7.62)] and metastasis [HR = 2.59 (1.29 - 5.60)] were independent predictors of VTE recurrence in the context of cancer-associated VTE\(^30\). Conversely, breast cancer [HR = 0.59 (0.17 - 2.01)] showed a trend towards 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 [RR = 1.36 (95%CI, 1.06-1.74; p = 0.01)], lung or gastrointestinal malignancies increasing the risk of recurrence and patients with breast cancer and hematological malignancies, presenting with a lower risk \(^13\).

Our 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 score which groups stages I and II as one variable appears to be less discriminatory than our original model, suggesting an advantage to classifying patients tumor stage as TNM stage I versus stage II, III and IV. Wasson \(^29\) published the methodological standards for Clinical Prediction Rules and later those standards were updated \(^24\). Wasson states that the outcome to be predicted must be clearly defined, 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, standardised, and their assessment was done without knowledge of the outcome which fulfils 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 since only 13% of patients had D-Dimer levels performed 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\textsuperscript{22,31-33}. They are likely to be soft outcomes for evaluation of recurrence since they most likely will reflect the impact of the anticancer treatment (chemotherapy/ radiation therapy) and could act as confounding in the VTE recurrence setting. Treatment strategy was not a predictor of recurrence. In our study, there was no difference in VTE recurrence rate according to treatment strategy [RR= 1.13 (95% CI, 0.743 - 1.711; p= 0.565)]. Furthermore, a subgroup analysis applying the clinical prediction rule to patients who used long-term VKA or who used long-term LMWH, demonstrated that our prediction tool worked accurately independent of treatment approach. Regardless, for a clinical prediction rule to be accurate and utile, it does not need to contain all possible independent predictors. Conversely, it has to be sensible, relevant, demonstrate face and content validity, be concise, and easy to use in the intended clinical application. Most importantly, 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 dataset, all recurrent events were accurately objectively diagnosed with clinical and imaging techniques and data was
prospectively collected.

In summary, regardless of using a three category score or dichotomized score, our model appears to differentiate risk for recurrence and could be utilized in treatment trials attempting novel treatment strategies in high risk patients since LMWH alone does not seem to be enough. For low risk patients a case could be made for using the less costly typical “LMWH followed by oral anticoagulants” 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, + 1 for lung cancer, female sex and previous VTE allows for predicting low risk for recurrent VTE when the score totals ≤ 0 and high risk if score > 0. Hopefully, 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 venous thromboembolism.

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**Conflict of Interest Disclosures:** In the last five years Dr. Rodger has received honoraria for presentations for Pfizer, Boehringer Ingelheim, GTC Therapeutics, Biomerieux and Leo Pharma. In the last five years, Dr. Wells has received honoraria for presentations for Bayer, Biomerieux, Sanofi Aventis and Boeringer Ingelheim.

**References:**


25. Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R, Rimm AA. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those


Table 1. Baseline characteristics of Derivation and Validation study samples

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>Derivation Study (n=543)</th>
<th>Validation Study (n=819)</th>
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<tbody>
<tr>
<td>Male/Female n (%)</td>
<td>240 / 303 (44/56)</td>
<td>392 / 427 (48/52)</td>
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<tr>
<td>Male n (%)</td>
<td>240 (44)</td>
<td>392 (48)</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>303 (56)</td>
<td>427 (52)</td>
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<tr>
<td>Primary Tumor Site</td>
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<tr>
<td>Lung n (%)</td>
<td>96 (17.7)</td>
<td>106 (12.9)</td>
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<tr>
<td>Breast n (%)</td>
<td>85 (15.6)</td>
<td>139 (17.0)</td>
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<tr>
<td>GI*</td>
<td>140 (25.8)</td>
<td>179 (21.9)</td>
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<tr>
<td>Other</td>
<td>164 (30.2)</td>
<td>309 (37.7)</td>
</tr>
<tr>
<td>Hematological</td>
<td>58 (10.7)</td>
<td>86 (10.5)</td>
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<tr>
<td>Prior VTE n (%)</td>
<td>46 (8.5)</td>
<td>96 (11.7)</td>
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<tr>
<td>TNM Stage** n(%)</td>
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<tr>
<td>I= 61 (12.6)</td>
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<td>I+II= 277 (37.8)</td>
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<tr>
<td>II= 74 (15.3)</td>
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<td>III = 84 (17.3)</td>
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<td>IV= 237 (48.9)</td>
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*GI: gastrointestinal; ** TNM (tumor- nodes- metastasis staging system) for solid tumors only: Derivation study (n=485) and Validation study (n=733)

Table 2. The Ottawa Score for Recurrent VTE risk in cancer-associated Thrombosis

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<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient</th>
<th>Points</th>
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<tbody>
<tr>
<td>Female</td>
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<tr>
<td>Lung cancer</td>
<td>0.94</td>
<td>1</td>
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<tr>
<td>Breast Cancer</td>
<td>-0.76</td>
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</tr>
<tr>
<td>TNM* Stage I</td>
<td>-1.74</td>
<td>-2</td>
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<tr>
<td>Previous VTE</td>
<td>0.40</td>
<td>1</td>
</tr>
<tr>
<td>Clinical Probability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&lt; or = 0)</td>
<td></td>
<td>-3 to 0</td>
</tr>
<tr>
<td>High (&gt; or = 1)</td>
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<td>1 to 3</td>
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* TNM (tumor- nodes- metastasis staging system) for solid tumors only
Table 3. The final score in the derivation and validation samples

<table>
<thead>
<tr>
<th>Sum of points</th>
<th>Derivation Study**</th>
<th>Validation Study**</th>
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<tr>
<td></td>
<td>Patients (n)</td>
<td>VTE recurrence (n)</td>
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<td>-2</td>
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<tbody>
<tr>
<td>Low (&lt; or = 0)</td>
<td>4.5%</td>
<td>Low (&lt; or = -1)</td>
<td>5.1%</td>
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<tr>
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<td>19.7%</td>
<td>Intermediate (zero)</td>
<td>9.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High (&gt; or = 1)</td>
<td>15.8%</td>
</tr>
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**Validation set: CLOTCAN group: CLOT trial and CANTHANOX trial dataset
* Derivation set: Ottawa retrospective study
Figure Legends:

**Figure 1.** Flowchart of eligible patients in the derivation set. Anticoagulation for other reason than VTE*: perioperative management of patients with cancer on anticoagulants due to atrial fibrillation or prosthetic heart valves; ISS**: isolated subsegmental PE; IVCF***: inferior vena cava filter

**Figure 2.** Cox proportional regression for evaluation of VTE recurrence risk in study sample (derivation model) according to temporal trend*
Potentially eligible patients (1237)

Excluded Patients (694)

Included Patients (543)

Reason for Exclusion

1. Anticoagulation for other reason than VTE* (315)
2. No confirmed diagnosis of VTE (153)
3. Superficial phlebitis or calf VTE (60)
4. ISS** (8)
5. Arterial Thrombosis (18)
6. No active cancer (121)
7. IVCF***, no anticoagulation (2)
8. Duplicate or non-existing chart number (19)
Development of a Clinical Prediction Rule for Risk Stratification of Recurrent Venous Thromboembolism in Patients with Cancer: Associated Venous Thromboembolism

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