Low discriminating power of the modified Ottawa VTE risk score in a cohort of patients with cancer from the RIETE registry

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Summary

Treatment of patients with cancer-associated venous thromboembolism (VTE) remains a major challenge. The modified Ottawa score is a clinical prediction rule evaluating the risk of VTE recurrences during the first six months of anticoagulant treatment in patients with cancer-related VTE. We aimed to validate the Ottawa score using data from the RIETE registry. A total of 11,123 cancer patients with VTE were included in the analysis. According to modified Ottawa score, 2,343 (21 %) were categorised at low risk for VTE recurrences, 4,525 (41 %) at intermediate risk, and 4,255 (38 %) at high risk. Overall, 477 episodes of VTE recurrences were recorded during the course of anticoagulant therapy, with an incidence rate for low, intermediate, and high risk groups of 6.88 % (95 % CI 5.31–8.77), 11.8 % (95 % CI 10.1–13.6), and 21.3 % (95 % CI 18.8–24.1) patient-years, respectively. Overall mortality had an incidence rate of 21.1 % (95 % CI 18.2–24.3), 79.4 % (95 % CI: 74.9–84.1), and 134.7 % (95 % CI: 128.3–141.4) patient-years, respectively. The accuracy and discriminating power of the modified Ottawa score for VTE recurrence was modest, with low sensitivity, specificity and positive predictive value, and a C-statistics of 0.58 (95 % CI: 0.56–0.61). In our analysis, the modified Ottawa score did not accurately predict VTE recurrence among patients with cancer-associated thrombosis, thus hindering its use in clinical practice. It is time to define a new score including other clinical predictors.

Keywords

Venous thromboembolism, venous thrombosis, recurrence, neoplasms, decision support techniques

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Introduction

Venous thromboembolism (VTE), which includes deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a major source of morbidity and mortality and a leading cause of death in cancer patients (1, 2). Patients with active cancer have four- to seven-fold increased risk of developing VTE compared to patients without cancer (1, 2). Following a first episode of VTE, the risk of recurrences is significantly higher in cancer patients and varies according to type of cancer, its localisation, and staging (2). Treatment of patients with cancer-associated VTE remains a major challenge. Currently, patients with cancer and a first episode of VTE are generally treated for 3–6 months with low-molecular-weight heparin (LMWH) injections as first choice agent (3, 4). This recommendation is based on results of reported superiority of LMWH over vitamin K antagonist (VKA) in reducing incidence of VTE recurrence with a relative risk reduction of 53 % (5).

VTE management beyond this first period of anticoagulation is still a matter of debate. Guidelines and expert consensus suggest continuing anticoagulant therapy in patients with active cancer, preferably always with LMWH (3, 4). This approach may be problematic for several reasons including burden of daily injections, risk of haematoma at injection site, bleeding in general, osteoporosis, and heparin-induced thrombocytopenia. The possibility to stratify patients according to their risk of VTE recurrence, would allow individualising therapeutic strategy (e.g. continuing indefinitely anticoagulant treatment in high-risk patients and, conversely, stopping anticoagulant therapy or using an alternative agent, as VKA or new direct oral anticoagulants, in low-risk patients). Recently, Louzada et al. proposed the Ottawa score, a clinical prediction rule to identify patients at risk of VTE recurrence during the first six months of

anticoagulant treatment (6). The original model was a dichotomised score (low or high risk for VTE recurrence) taking into account the TNM classification as a variable. Subsequently, because of missing TNM classification informations in the validation study, an adjusted model combining TNM stage I+II (corresponding to patients without metastatic disease) and TNM stage III +IV (patients with metastases) was proposed. In this modified form anticoagulated patients with active cancer and VTE were classsified in low, intermediate, and high risk categories of VTE recurrence during the first six months of treatment (6). Reproducibility of this modified Ottawa score was confirmed in a Dutch (7) and a French study (8) assessing 419 and 235 patients, respectively; but not in a sub-analysis from the CATCH study evaluating 900 patients with cancer-associated thrombosis (9). A further study, by Ahn et al. failed to validate the score in its original version (10).

Assuming that these conflicting results were due to low discriminating power of the score, we decided to perform a further evaluation of the Ottawa score on a large sample size, using data from the RIETE registry (Registro Informatizado de la Enfermedad TromboEmbólica) (11, 12). We aimed to assess the prognostic value of the modified Ottawa score in predicting the likelihood of VTE recurrences during the first six months of anticoagulant treatment. As secondary objective, we evaluated the ability of the score to predict both overall mortality and fatal PE rate.

Methods

RIETE registry

RIETE is an ongoing multicenter, prospective registry of consecutive patients presenting with symptomatic acute VTE confirmed by objective testing (11, 12). Objective imaging for VTE included compression ultrasonography or contrast venography for DVT, and helical computed tomography-scan, ventilation-perfusion lung scintigraphy, or angiography for PE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their relatives) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

Data were recorded on an electronic case report form at each participating site and submitted to a centralised coordinating centre through a secure website. Data quality was regularly monitored for accuracy electronically and by periodic visits to participating sites. Inconsistencies were resolved by contacting the local coordinators who corrected forms with source data. Histologic proof of cancer was always required. Patients enrolled in the RIETE registry had data collected from the time of VTE diagnosis that included: age; sex; weight; anticoagulant therapy, documentation of chronic heart or lung disease; recent (<30 days before VTE) major bleeding; recent immobility (defined as nonsurgical patients assigned to bed rest with bathroom privileges for >4 days in the 2 months before VTE diagnosis); surgery (defined as those who had undergone major surgery in the 2 months before VTE clinical signs and symptoms on admission (dyspnea, chest pain, haemoptysis, syncope, painful and/or swollen limb), heart rate, systolic blood pressure levels, hemoglobin level, white cell count, platelet count, and serum creatinine levels at baseline.

Patients were managed according to the current clinical practice of each participating site (i.e. there was no standardisation of treatment). The type, dose, and duration of anticoagulant therapy were recorded.

During each visit, any signs or symptoms suggesting symptomatic VTE or major bleeding was noted. Recurrent VTE was defined as a DVT in a new segment, a DVT 4 mm larger in diameter when compared to prior venous ultrasound (13), a new ventilation-perfusion mismatch in a lung scan, or a new intraluminal-filling defect on a CT scan (14). Major bleeding was defined as an overt bleed that required a transfusion of two or more units of blood, was retroperitoneal, spinal or intracranial, or was fatal. Fatal bleeding or fatal VTE were defined as any death occurring within 10 days of a corresponding event, in the absence of an alternative cause of death.

Ottawa score

The modified Ottawa score was calculated as previously described (6). Patients received +1 point for being a woman, +1 point for having lung cancer, and +1 point for prior VTE. Patients received –1 point for having breast cancer, and –1 point for having localised cancer without metastasis (stages 1 and 2 for solid tumours). Patients did not receive additional points for having a haematologic malignancy. Clinical probability of recurrence was defined as low if the score was less than or equal to –1, intermediate if the score was 0, and high if the score was ≥1.

Study design and analysis

Consecutive patients with acute symptomatic, objectively confirmed VTE and concomitant active cancer were included in the analysis. Active cancer was defined as any solid (excluded basal-cell or squamous-cell carcinoma of the skin) or haematologic malignancy discovered within six months prior and four weeks following VTE diagnosis. Other definitions included local or metastatic diffusion, ongoing, or within the last six months, chemotherapy, cancer-related hormonotherapy.

According to the modified Ottawa score, patients were stratified in three risk categories: low, intermediate, and high risk. We calculated the incidence of the following variables: recurrent DVT, recurrent PE, recurrent VTE, overall mortality, and fatal PE, during the first six months of anticoagulant treatment and following discontinuation. Results are presented as events per 100 patient-year rates. Differences between three risk groups were assessed using Student's t-test and Chi^2 test (or Fisher's when frequency low) as appropriate. In order to make a comparison with previous studies, we also estimated the cumulative rates of VTE recurrences during the first six months by Kaplan-Maier method and compared by use of a log rank test. Furthermore, to assess accuracy of the modified Ottawa score to predict VTE recurrence and overall mortality during the first six months of anticoagulation, we calculated sensitivity, specificity, positive predictive values (PPV) and

Table 1: Patient characteristics.

	Overall (11,123)	Low risk (2,343)	Intermediate risk (4,525)	High risk (4,255)
Age, mean ± SD	67 ± 13	68 ± 13	68 ± 13	67 ± 13‡
Female sex, n (%)	5,145 (46 %)	624 (27 %)	1,598 (35 %)‡	2,923 (69 %)‡
BMI, mean ± SD	27 ± 5	27 ± 5	27 ± 5‡	26 ± 5‡
Index VTE,				
Lower extremities proximal DVT, n (%)	6,947 (91 %)	1,443 (89 %)	2,882 (92 %)‡	2,622 (91 %)*
PE, n (%)	5,501 (49 %)	1,127 (48 %)	2,200 (49 %)	2,174 (51 %)*
Anticoagulation				
LMWH, n (%)	7,060 (63 %)	1,245 (53 %)	2,900 (64 %)‡	2,915 (69 %)‡
VKA, n (%)	2,987 (27 %)	984 (42 %)	1,176 (26 %)‡	827 (19 %)‡
Fondaparinux, n (%)	129 (1.2 %)	14 (0.60 %)	50 (1.1 %)*	65 (1.5 %)‡
Unfractioned heparin, n (%)	64 (0.58 %)	11 (0.47 %)	28 (0.62 %)	25 (0.59 %)
DOACs, n (%)	84 (0.76 %)	29 (1.2 %)	32 (0.71 %)*	23 (0.54 %)†
Previous VTE, n(%)	1,347 (12 %)	4 (0.17 %)	343 (7.6 %)‡	1,000 (24 %)‡
Inpatients, (%)	3,282 (30 %)	689 (30 %)	1,340 (30 %)	1,253 (30 %)
Primary tumour site, n (%)				
Lung	1,691 (15 %)	0	222 (4.9 %)‡	1,469 (35 %)‡
Breast	1,407 (13 %)	660 (28 %)	656 (14 %)‡	91 (2.1 %)‡
Colorectal	1,561 (14 %)	295 (13 %)	752 (17 %)‡	514 (12 %)
Other GI site	1,316 (12 %)	155 (6.6 %)	639 (14 %)‡	522 (12 %)‡
Gynaecologic	849 (7.6 %)	0	218 (4.8 %)‡	631 (15 %)‡
Other solid tumour	3,500 (31 %)	1,151 (49 %)	1,651 (36 %)‡	698 (16 %)‡
Haematologic	799 (7.2 %)	82 (3.5 %)	387 (8.6 %)‡	330 (7.8 %)‡
Metastatic disease, n (%)	6,127 (55 %)	12 (0.51 %)	2,569 (57 %)‡	3,546 (83 %)‡
Ongoing chemotherapy or chemotherapy in the last 6 months, n (%)	5,812 (52 %)	1,282 (55 %)	2,390 (53 %)	2,140 (50 %)‡
Hormone therapy cancer-related, n (%)	1,161 (10 %)	558 (24 %)	465 (10 %)‡	138 (3.2 %)‡

Differences between patients at intermediate or high risk vs those at low risk: *p <0.05; †p <0.01; ‡p <0.001. SD, standard deviation; BMI, body mass index; VTE, venous thromboembolism; DVT, deep-vein thrombosis; PE, pulmonary embolism; LMWH: Low-molecular-weight heparin; VKA: Vitamin K antagonists; DOAC: Direct Oral Anticoagulants; GI, gastrointestinal.

negative predictive values (NPV), likelihood ratios. Finally, we evaluated the discriminating power of the score to predict VTE recurrence and overall mortality during the first six months of anticoagulant treatment by calculating the area under the receiver-operating characteristic (ROC) curve. All statistical analyses were performed using the IBM SPSS Statistics program (version 19; SPSS Inc., Chicago, IL, USA).

Results

At time of our analysis (September 1, 2016) 66,403 patients were included in RIETE. Of these, 11,123 (17 %) had active cancer. Patients' stratification according to the modified Ottawa score categorised 2,343 (21 %) patients in the low-risk group for VTE recurrences; 4,525 (41 %) in the intermediate-risk group, and 4,255 (38 %) in the high-risk group. Patients' characteristics at baseline and type of anticoagulant used are reported in ▶Table 1. We observed no difference in the distribution of DVT and PE among three risk groups. About half of the patients had metastatic cancer and/or were under chemotherapy. Metastases were significantly more frequent in the intermediate- and high-risk groups than in the low-risk group. Conversely, chemotherapy and hormonotherapy were significantly more frequent in the low-risk group rather than in the high-risk group. About two thirds of patients, mainly in the intermediate- and high-risk group, received long-term therapy with LMWH.

Considering the first six months of anticoagulant therapy, duration of treatment prior to VTE recurrences in the three groups

Table 2: Stratification of patients according to modified Ottawa score during the first six months of anticoagulant therapy.

	Low risk		Intermediate risk		High risk	
	N	N per 100 patient-years	N	N per 100 patient-years	N	N per 100 patient-years
Patients, N	2,343		4,525		4,255	
Duration (mean days)	140 ± 50		118 ± 61‡		103 ± 63‡	
Median days(IQR)	176 (101–180)		122 (77–180) ‡		102 (41–180)‡	
Events						
Recurrent DVT	31	3.47 (2.40–4.86)	96	6.67 (5.43–8.11)‡	119	10.1 (8.37–12.0)‡
Recurrent PE	30	3.36 (2.31–4.73)	78	5.40 (4.30–6.71)*	132	11.2 (9.38–13.2)‡
Recurrent VTE	61	6.88 (5.31–8.77)	168	11.8 (10.1–13.6)‡	248	21.3 (18.8–24.1)‡
Overall mortality	190	21.1 (18.2–24.3)	1156	79.4 (74.9–84.1)‡	1619	134.7 (128.3–141.4)‡
Fatal PE	15	1.67 (0.97–2.69)	108	7.42 (6.11–8.92)‡	111	9.24 (7.64–11.1)‡

Differences between patients at intermediate or high risk vs those at low risk: *p <0.05; †p <0.01; ‡p <0.001. IQR, interquartile range; DVT, deep-vein thrombosis; PE, pulmonary embolism.

Table 3: Stratification of patients according to modified Ottawa score after discontinuation of anticoagulant therapy.

	Low risk		Intermediate risk		High risk	
	N	N per 100 patient-years	N	N per 100 patient-years	N	N per 100 patient-years
Patients, N	819		1,244		1,011	
Duration (mean days)	387 ± 581		284 ± 458‡		195 ± 327‡	
Median days (IQR)	163 (53–475)		101 (26–339)‡		67 (16–224)‡	
Events						
Recurrent DVT	38	4.41 (3.17–6.00)	69	7.18 (5.63–9.03)*	61	11.4 (8.78–14.5)‡
Recurrent PE	30	3.47 (2.38–4.89)	48	5.00 (3.73–6.57)	35	6.50 (4.60–8.94)*
Recurrent VTE	68	7.93 (6.20–9.99)	117	12.2 (10.2–14.6)†	96	17.9 (14.6–21.8)‡
Overall mortality	95	10.9 (8.90–13.3)	393	40.6 (36.8–44.8)‡	462	85.5 (78.0–93.6)‡
Fatal PE	1	0.12 (0.01–0.57)	4	0.41 (0.13–1.00)	5	0.93 (0.34–2.05)*

Differences between patients at intermediate or high risk vs those at low risk: *p <0.05; †p <0.01; ‡p <0.001. IQR, interquartile range; DVT, deep-vein thrombosis; PE, pulmonary embolism.

was 140 ± 50 days (median: 176; interquartile range [IQR] 101–180); 118 ± 61 days (median 122; IQR 77–180), and 103 ± 63 days (median 102; IQR 41–180), for low-, intermediate- and high-risk gropus, respectively. Overall, 477 episodes of VTE recurrences were recorded (237 as recurrent DVT, 240 as recurrent PE). Of these, 61 occurred in the low-risk group corresponding to an incidence rate of 6.88% per patient-year (95% confidence interval [CI] 5.31–8.77); 168 in the intermediate-risk (11.8% per patient-year; 95% CI 10.1–13.6), and 248 in the high-risk group (21.3% per patient-year; 95% CI 18.8–24.1). Differences between the three risk groups was statistically significant (p<0,001, ▶Table 2). Similar statistically significant differences were observed for overall mortality (21.1%, 79.4% and 134.7% per patient-year, respectively, p<0,001), and for all other parameters considered (▶Table 2). These differences remained also after discontinuation of anticoagulant therapy (▶Table 3).

According to Kaplan-Maier method, cumulative incidence of VTE recurrence at six months was 2.9%, 4.8%, and 8.2% for low-, intermediate-, and high-risk patients, respectively (p<0.001). However, the prognostic performance of the Ottawa score for VTE recurrences showed low sensitivity, specificity, PPV, and accuracy with a C-statistic of 0.58 (95%CI: 0.56–0.61) (▶Table 4). Similar results were obtained when evaluating prediction for overall mortality with a C-statistic slightly better (0.65; 95%CI: 0.64–0.66) (▶Table 4).

Discussion

We demonstrated, in a large cohort of consecutive patients with cancer-associated VTE, that the modified Ottawa score has a modest discriminating power and therefore it is not able to accurately predict the risk of VTE recurrences. This results contrasts

	Low risk (-1 points)	Intermediate risk (0 points)	High risk (≥1 points)
Patients, N	2,343	4,525	4,255
VTE recurrent	61	168	248
Sensitivity	12.8 (9.79–15.8)	35.2 (30.9–39.5)	52.0 (47.5–56.5)
Specificity	78.6 (77.8–79.3)	59.1 (58.1–60.0)	62.4 (61.4–63.3)
Positive predictive value	2.60 (1.96–3.25)	3.71 (3.16–4.26)	5.83 (5.12–6.53)
Negative predictive value	95.3 (94.8–95.7)	95.3 (94.8–95.8)	96.7 (96.2–97.1)
Positive likelihood ratio	0.60 (0.52–0.68)	0.86 (0.81–0.92)	1.38 (1.31–1.46)
Negative likelihood ratio	1.11 (1.07–1.15)	1.10 (1.02–1.17)	0.77 (0.70–0.85)
Accuracy	75.7 (74.9–76.5)	58.0 (57.1–59.0)	61.9 (61.0–62.8)
AUC ROC	0.46 (0.43–0.48)	0.47 (0.45–0.50)	0.57 (0.55–0.60)
AUC ROC (scored by categories)	0.58 (0.56–0.61)		
Overall mortality	190	1,156	1,619
Sensitivity	6.41 (5.53–7.29)	39.0 (37.2–40.7)	54.6 (52.8–56.4)
Specificity	73.6 (72.6–74.6)	58.7 (57.6–59.8)	67.7 (66.7–68.7)
Positive predictive value	8.11 (7.00–9.21)	25.5 (24.3–26.8)	38.0 (36.6–39.5)
Negative predictive value	68.4 (67.4–69.4)	72.6 (71.5–73.7)	80.4 (79.5–81.3)
Positive likelihood ratio	0.24 (0.23–0.26)	0.94 (0.91–0.98)	1.69 (1.60–1.79)
Negative likelihood ratio	1.27 (1.25–1.29)	1.04 (1.00–1.08)	0.67 (0.64–0.70)
Accuracy	55.7 (54.8–56.6)	53.4 (52.5–54.4)	64.2 (63.3–65.1)
AUC ROC	0.40 (0.39–0.41)	0.49 (0.48–0.50)	0.61 (0.60–0.62)
AUC ROC (scored by categories)	0.65 (0.64–0.66)		

AUC ROC denotes area under ROC (receiver operating characteristic) curve.

Table 4: Diagnostic characteristics of Ottawa score to predict outcome during first six months of treatment.

with some previously published data. Indeed, Den Exter et al. (7) found a statistically significant difference of incidence of VTE recurrences for low-, intermediate-, and high-risk groups (2.4%, 8.8%, 15.9%, respectively, p= 0.03). These results have been confirmed by Astruc et al (8) with an incidence of 2.6%, 8.6%, and 24.9% (p=0.02). Our data are in accordance with those from the sub-analysis of the CATCH trial that is the largest randomised clinical trial to date among patients with cancer-associated thrombosis (9). However, in all these studies the authors evaluated the difference in incidence of VTE recurrences among the various risk groups without really assessing the performance of the score. We assumed that these contrasting results were due to low discriminating power of the score and we performed a further analysis evaluating the performance of the test.

In the present study, a statistically significant increase in the rate of VTE recurrences was observed in the intermediate- and high-risk groups. However, the 8.2% incidence for high-risk group is lower than that previously found corresponding to values of the intermediate-risk group in previous studies (7, 8). Moreover and importantly, this association does not correspond to an accurate prediction. Indeed, accuracy and discriminating power of the modified Ottawa score is modest resulting in very low sensitivity, specificity and PPV with an area under the ROC curve not much different from chance alone (►Table 4). Although NPV was proportionally high, a score allowing an annual recurrence rate of about 6% in the low-risk population is not clinically relevant. Such a recurrence rate is in line with that expected for non-provoked VTE, for which accepted practice is to continue secondary prophylaxis (3, 15).

Identifying clinical predictors for VTE recurrence, in order to stratify patients with cancer-associated VTE, remains a priority for adequate management. In the last years, other clinical predictors were proposed. Trujillo-Santos et al. showed that patients aged <65 years, with a diagnosis of cancer <3 months, and clinically overt PE were at high risk for VTE recurrence (16). Napolitano et al. proposed residual vein thrombosis to predict risk of VTE recurrence in cancer patients (17). Recently, Khorana et al. suggested venous compression from tumour mass or adenopathy, and a diagnosis of hepatobiliary cancer as predictors (9). Unfortunately, neither of these parameters has yet been externally validated.

We note that 27% of the studied cohort had colorectal and breast cancer, usually considered as low risk for VTE. However, less than 50% of brest cancer and less than 20% of colorectal cancer were classified as low risk for recurrent VTE. Conversely, chemotherapy and hormone therapy, usually considered a risk factor for VTE recurrence, were significantly more frequent in the

low-risk group than in the high-risk group. We observed that a proportion of deaths were significantly increased in the intermediate- and high-risk groups. However, only 109 of 1156 (9.4%) deaths among patients in the intermediate group, and about 111/1169 (6.8%) of deaths in the high-risk group, were due to fatal PE. Therefore, this association is not predictive of fatal thrombotic event. In addition, once again, this association does not correspond to an accurate prediction of mortaliy after cancer-associated thrombosis. The performance of the score remains inadequate with low specificity and PPV and an area under the ROC curve not much different from that obtained with random flipping of a coin (▶Table 4).

To our knowledge this is the first analysis of prognostic performance of the modified Ottawa score. In addition, we used the largest database among patients with cancer-associated thrombosis. Finally, our analysis reflects real-world management and is not limited to a selected population as in previous studies.

In conclusion, in our analysis the modified Ottawa score did not accurately predict VTE recurrence among patients with cancer-associated thrombosis. Thus, it could lead to erroneous clinical decision. It is therefore necessary to derive a new score.

Appendix

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Author contributions

A. Alatri and L. Mazzolai designed the study. All authors collected data. A. Alatri, L. Mazzolai and M. Monreal analysed data. A. Alatri draft the manuscript. All authors revised manuscript and agreed to the final version.

Conflicts of interest

None declared.

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