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The Ottawa score performs poorly in cancer patients with incidental pulmonary embolism

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ABSTRACT

Background: The Ottawa score was previously developed to predict recurrent venous thromboembolism (VTE) in cancer patients with VTE. The performance of this score in patients with incidental VTE is currently unclear.
Aim: To evaluate the performance of the Ottawa risk score in cancer patients with incidental pulmonary embolism included in an international, prospective, observational cohort study.
Methods: The score was used to classify patients as high (≥ 1), intermediate (0), or low risk (≤ -1). The discriminative performance of the score was estimated by calculating the cumulative incidence of recurrent VTE for all groups, the time-dependent c-statistic, and the sub-distribution hazard ratio (SHR), using a competing risk approach.
Results: Of the 691 patients for which the Ottawa score could be calculated, 25 (3.6%) had recurrent VTE during 6-month follow-up and 38 (5.5%) during 12-month follow-up. The c-statistics of the continuous score at 6 and 12 months were 0.45 (95% CI, 0.36–0.54) and 0.51 (95% CI, 0.46–0.59), respectively. The 6-month cumulative incidences of recurrent VTE for those at low, intermediate, and high risk were 3.9% (95% CI, 1.5–8.4), 3.6% (95% CI, 1.9–6.2), and 3.6% (95% CI, 1.8–6.5), respectively. A sensitivity analysis restricted to the on-treatment period yielded similar results. None of the Ottawa risk score items were significantly associated with recurrent VTE.
Conclusion: In cancer patients with incidental pulmonary embolism, the Ottawa risk score has a poor predictive value for recurrent VTE, which does not support the use of the score in this patient population.

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1. Introduction

Cancer patients with venous thromboembolism (VTE) are at increased risk of recurrent VTE compared with patients without cancer, despite anticoagulant therapy. The 6-month incidence of recurrent VTE after an initial VTE event is reported to be up to 9% during treatment with low-molecular-weight heparins in the setting of acute symptomatic cancer-associated thrombosis [1,2]. Recurrent VTE is a serious complication as it is associated with significant morbidity and worse survival [3,4]. Current guidelines recommend at least 6 months of anticoagulant therapy as secondary prevention for cancer-associated VTE [5,6]. Although it is suggested to extend treatment as long as the cancer is active, scant data are available to guide treatment continuation beyond the initial 6-month treatment phase. In addition, there is uncertainty whether a dose reduction beyond the first month is appropriate to avoid excessive bleeding. These decisions of anticoagulant treatment type, dosage, and duration should include a balanced evaluation of both the risk of recurrent VTE and bleeding during treatment.

Previously, the Ottawa risk score has been introduced with the aim to select cancer patients at high risk of recurrent VTE during anticoagulant treatment [7]. This tool could be used to guide individualized treatment, for instance by intensifying or prolonging treatment in those at high risk of recurrent VTE or stopping anticoagulation in patients at low risk. The score was derived in a retrospective cohort of cancer patients with symptomatic VTE mostly treated with low-molecular-weight heparin, and includes several readily available clinical variables. The score assigns patients to a low-risk group with a 6-month recurrent VTE risk of approximately 4.5% in the derivation cohort, and a high-risk group with a risk of about 19%. Initial external validation by the same authors, in which a modified score was used trichotomously by creating a low, intermediate, and high-risk group, showed comparable outcomes [7]. However, subsequent cohort studies have reported conflicting results with regard to the score's discriminatory performance [8–11]. Consequently, current guidelines have not endorsed the score for use in clinical practice [5,6].

Besides the Ottawa score, several other possible predictors of recurrent VTE in cancer patients have been identified, including body weight [4], creatinine clearance < 30 mL/min [4], younger age [4], histological cancer type [12], and residual vein thrombosis [13]. It is unclear whether other variables such as chemotherapy or hormonal therapy type are also predictive of recurrent VTE.

As the derivation and validation studies of the Ottawa risk score did not include patients with incidental VTE, the discriminatory performance of the score in these patients is currently unknown. The aim of the present analysis was to assess the discriminatory performance of the modified Ottawa risk score and to identify other risk factors predictive of recurrent VTE in patients with active cancer and incidentally detected pulmonary embolism (PE) [14].

2. Methods

2.1. Study design

The UPE study was an international, prospective, observational cohort study including 695 cancer patients with incidentally detected PE (ClinicalTrials.gov; NCT01727427). The study design and methods were previously described in detail [14]. Briefly, cancer patients with PE incidentally detected on routine contrast-enhanced CT-scans were followed for 12 months for recurrent VTE, major bleeding, and all-cause mortality. Outcomes were centrally adjudicated by an adjudication committee.

2.2. Study outcomes

The primary outcome of the current analysis was recurrent VTE, defined as objectively confirmed recurrent symptomatic or incidental lower-extremity deep-vein thrombosis (distal or proximal), PE, or PE-related death. Death was considered to be related to PE if the PE was objectively confirmed by imaging tests shortly before death, by autopsy, or in case of an unexplained sudden death for which PE could not be ruled out.

2.3. Ottawa risk score

The modified Ottawa score was computed for each patient based on the following clinical characteristics at baseline: female sex (+1 point), lung cancer (+1 point), breast cancer (−1 point), non-metastatic cancer (−1 points), and prior VTE (+1 point). Following other validation studies, non-metastatic disease was used as a proxy for tumor node metastasis (TNM) stage I or II, since TNM staging information was not routinely collected in the present study [8]. Patients were classified as 'low risk' (≤ −1 point), 'intermediate risk' (0 points), or 'high risk' (≥1 point) using the previously proposed cut-offs [7]. In an additional analysis, the score was evaluated dichotomously by assigning −2 points for non-metastatic disease, and classifying patients to a low-risk group (≤0 points) or high-risk group (≥1 points).

2.4. Statistical analysis

Descriptive statistics were used to assess baseline characteristics. The cumulative incidence of recurrent VTE for low, intermediate, and high-risk patients according to the modified Ottawa score was estimated using the cumulative incidence function proposed by Fine and Gray, in which death not related to PE was treated as a competing event for recurrent VTE [15]. The discriminatory performance of the continuous Ottawa score was assessed by estimating the time-dependent c-index, while accounting for the competing risk of death. Corresponding 95% confidence intervals (CI) were calculated by repeating the analyses in 250 bootstrap samples [16].

The association between potential risk factors, previously identified in literature, and recurrent VTE was evaluated by estimating sub-distribution hazard ratios (SHR) in a univariable Fine & Gray competing risk model. The proportionality assumption was checked by visual inspection of the Schoenfeld residuals. All outcomes were estimated at 6 and 12 months after the index PE. A sensitivity analysis restricted to the on-treatment period, defined as the time during anticoagulant therapy and up to 7 days after discontinuation, was performed. A P-value below 0.05 was considered to indicate statistical significance. All analyses were performed in R v3.5.1 (The R Foundation for Statistical Computing, www.R-project.org) using the 'cmprsk' v.2.2-7 package for competing risk analyses, and the 'pec' package for the time-dependent c-statistic.

3. Results

3.1. Baseline characteristics

A total of 695 patients with active cancer and incidental PE were included in the UPE study. The Ottawa score could be computed for 691 of 695 patients (99.4%). One of the 4 patients for whom the score could not be calculated had recurrent VTE. Of the other 691 patients, 25 (3.6%) had recurrent VTE during 6-months follow-up and 38 (5.5%) during 12-months follow-up. Out of these 38 recurrent VTE, 22 events (56%) were recurrent PE with or without DVT, 10 (26%) were DVT only, and 7 (18%) were PE-related deaths. On-treatment recurrent VTE occurred in 24 (3.5%) patients in the first 6 months and in 32 (4.6%) during the 12-month period. During the 12-month follow-up period, 276 (40%) patients died and 36 (5.2%) were lost to follow-up.

Patient characteristics are presented in Table 1. The median age was 67 years, 42% of patients were female, and the median Karnofsky performance score was 80. The most frequent tumor types were gastrointestinal (39%), lung (15%), and urogenital (13%). The most

Table 1
Baseline characteristics of patients with and without recurrent VTE.

	Total study population (n = 695)	Patients without recurrent VTE (n = 656)	Patients with recurrent VTE (n = 39)	P-value
Age, median (IQR)	67.0 (59–75)	67.0 (60–75)	67.0 (58–74)	0.58
Female sex, n (%)	290 (41.7)	271 (41.3)	19 (48.7)	0.65
BMI, median (IQR)	24.7 (21.9–28.0)	24.8 (21.9–28.0)	24.5 (21.8–27.7)	0.90
Creatinine clearance mL/min, median (IQR)	76 (60–90)	76 (60–90)	80 (61–90)	0.73
Leukocyte count x 10^9/L, median (IQR)	6.4 (4.9–9.1)	6.5 (4.9–9.2)	6.1 (4.7–7.8)	0.36
Platelet count x 10^9/L, median (IQR)	229 (167–295)	229 (167–296)	221 (169–258)	0.58
Karnofsky performance scale, median (IQR)	80 (70–90)	80 (70–90)	90 (70–90)	0.29
Treatment for initial PE, n (%)				0.39
LMWH	600 (86.3)	567 (86.4)	33 (84.6)	
VKA	16 (2.3)	15 (2.3)	1 (2.6)	
DOACs	36 (5.2)	34 (5.2)	2 (5.1)	
Aspirin	3 (0.4)	2 (0.3)	1 (2.6)	
Fondaparinux	11 (1.6)	11 (1.7)	0 (0.0)	
Unfractionated heparin	9 (1.3)	9 (1.4)	0 (0.0)	
No treatment	20 (2.9)	18 (2.7)	2 (5.1)	
Previous VTE, n (%)	69 (9.9)	65 (9.9)	4 (10.3)	0.97
Most proximal extent of index PE, n (%)				
Central	100 (14.4)	93 (14.2)	7 (17.9)	0.68
Lobar	285 (41.0)	273 (41.6)	12 (30.8)	0.24
Segmental	238 (34.2)	222 (33.8)	16 (41.0)	0.46
Subsegmental	63 (9.1)	59 (9.0)	4 (10.3)	1.00
Central venous catheter, n (%)	181 (26.0)	173 (26.4)	8 (20.5)	0.70
Primary tumor site, n (%)				0.71
Breast	46 (6.6)	43 (6.6)	3 (7.7)	
Gastrointestinal	271 (39.0)	256 (39.0)	15 (38.5)	
Gynecological	71 (10.2)	66 (10.1)	5 (12.8)	
Hematological	25 (3.6)	25 (3.8)	0 (0.0)	
Lung	104 (15.0)	101 (15.4)	3 (7.7)	
Melanoma	20 (2.9)	18 (2.7)	2 (5.1)	
Urogenital	89 (12.8)	83 (12.7)	6 (15.4)	
Other	69 (9.9)	64 (9.8)	5 (12.8)	
Cancer treatment, n (%)[a]				
Chemotherapy (%)	374 (53.8)	357 (54.4)	17 (43.6)	0.40
Radiotherapy (%)	47 (6.8)	46 (7.0)	1 (2.6)	0.54
Hormone therapy (%)	37 (5.3)	35 (5.3)	2 (5.1)	0.97
Erythropoiesis stimulating agents (%)	9 (1.3)	8 (1.2)	1 (2.6)	0.75
Leucocyte stimulating agents (%)	24 (3.5)	22 (3.4)	2 (5.1)	0.82
Metastatic disease, n (%)	448 (64.5)	423 (64.5)	25 (64.1)	0.238

Abbreviations: BMI, body mass index; DOACs, direct oral anticoagulants; IQR, interquartile range, LMWH, low-molecular-weight heparins; PE, pulmonary embolism; SD, standard deviation; VKA, vitamin K antagonists.
[a] Cancer treatment in the 4 weeks prior to the index incidental PE event.

proximal extent of the index PE was in the central arteries in 100 patients (14%), lobar in 285 (41%), segmental in 238 (34%), and subsegmental in 63 (9%). The index incidental PE event was treated with low-molecular-weight heparin in 600 patients (86%), vitamin K antagonists in 16 (2%), direct oral anticoagulants in 36 (5%), and 20 (3%) received no anticoagulant treatment. There were no significant differences between patients with and without recurrent VTE (Table 1).

3.2. Performance of the Ottawa risk score

The group with a low-risk score comprised 128 patients (18.5%), intermediate-risk score 307 patients (44.4%), and high-risk score 256 patients (37.1%). The time-dependent c-statistics, which reflect the discriminatory performance of the continuous Ottawa score, were 0.45 (95% CI, 0.36–0.54) at 6 months and 0.51 (95% CI, 0.46–0.59) at 12 months. During the first 6 months, recurrent VTE was diagnosed in 5 patients (3.9%) in the low-risk group, in 11 (3.6%) in the intermediate-risk group, and in 9 (3.5%) in the high-risk group. The corresponding 6-month cumulative incidences for those at low, intermediate, and high risk were 3.9% (95% CI, 1.5–8.4), 3.6% (95% CI, 1.9–6.2), and 3.6% (95% CI, 1.8–6.5), respectively. The differences between the groups, reflected by the subdistribution hazard ratios were not significant (Table 2).

During the 12-month study period, 10 patients (7.8%) had recurrent VTE in the low-risk group, 14 (4.6%) in the intermediate-risk group, and 14 (5.5%) in the high-risk group. The corresponding cumulative incidences for patients at low, intermediate, and high risk were 8.2% (95% CI, 4.2–14.0), 4.9% (95% CI, 2.8–7.9), and 6.0% (95% CI, 3.4–9.5), respectively. As for the 6-month period, differences between these groups were not significant (Table 2). The time-to-event curves for the 12-month period are depicted in Fig. 1. The sensitivity analysis restricted to the on-treatment period yielded similar results (Supplementary Table 1). When using the Ottawa score dichotomously, the 6-month cumulative incidence of recurrent VTE was 3.6% (95% CI, 2.1–5.6) in the low-risk group (< 0 points), and 3.9% (95% CI, 1.9–7.0) in the high-risk group (Supplementary Tables 3 and 4).

3.3. Potential risk factors for recurrent VTE

In univariable regression analysis, none of the Ottawa risk score items and potential risk factors for recurrent VTE were significantly associated with recurrent VTE (Supplementary Table 2).

4. Discussion

The current study shows that the modified Ottawa score is not able to predict recurrent VTE in cancer patients with incidental PE. Overall discriminative performance of the continuous score was poor, as reflected by the c-statistic of 0.45 at 6 months and 0.51 at 12 months. The 6-month cumulative incidence of recurrent VTE was comparable in patients with a low, intermediate, and high-risk score (3.9%, 3.6%, and 3.6%, respectively). None of the risk factors previously identified in

Table 2
Risk of recurrent VTE in the Ottawa risk groups.

	Low-risk Ottawa score (≤ −1 points) N = 128	Intermediate-risk Ottawa score (0 points) N = 307	High-risk Ottawa score (≥1 points) N = 256
6-Month follow-up period			
Patients with recurrent VTE	5 (3.9%)	11 (3.6%)	9 (3.5%)
Cumulative incidence of recurrent VTE (95% CI)*	3.9% (1.5–8.4)	3.6% (1.9–6.2)	3.6% (1.8–6.5)
Subdistribution hazard ratio(95% CI)	Reference	0.9 (0.3–2.6)	0.9 (0.3–2.7)
12-Month follow-up period			
Patients with recurrent VTE	10 (7.8%)	14 (4.6%)	14 (5.5%)
Cumulative incidence of recurrent VTE (95% CI)*	8.2% (4.2–14.0)	4.9% (2.8–7.9)	6.0% (3.4–9.5)
Subdistribution hazard ratio (95% CI)	Reference	0.6 (0.3–1.3)	0.7 (0.3–1.6)

Abbreviations: CI, confidence interval; VTE, venous thromboembolism.

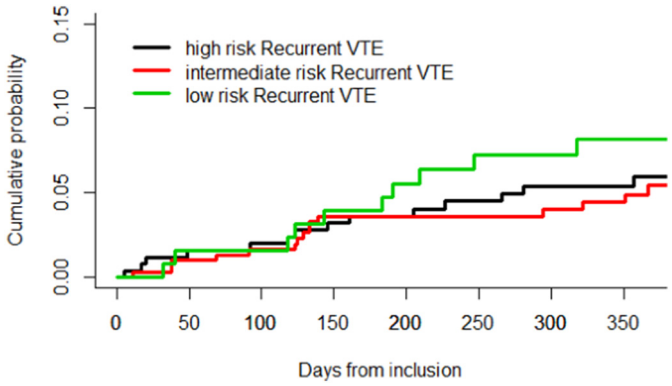

Fig. 1. Cumulative incidence of recurrent VTE in patients with a low, intermediate, and high-risk score according to the modified Ottawa score.

literature were significantly associated with recurrent VTE (Supplementary Table 2).

The Ottawa score stratifies patients with cancer-associated VTE based on their risk of recurrent VTE. It was derived in a retrospective cohort of 543 patients treated with anticoagulants for cancer-associated VTE and subsequently externally validated in two randomized controlled trials that compared vitamin K antagonists with low-molecular-weight heparin for cancer patients with VTE [7]. Using the score, clinicians may individualize anticoagulant treatment by, for example, intensifying treatment in those at high risk or limiting the treatment duration in those at low risk. The c-statistic in current analysis was 0.44 indicating a poor overall discriminative performance of the Ottawa risk score. In addition, cumulative incidence of recurrent VTE in the three risk groups appeared to be comparable at 6 and 12 months.

These findings are in line with previous studies that reported a modest performance of the score in patients with symptomatic VTE [10,11,17,18]. Alatri and colleagues evaluated the modified Ottawa score in a large prospective cohort of cancer patients with symptomatic VTE. The c-statistic after 6 months of follow-up was 0.58 (95% CI, 0.56–0.61). The 6-month cumulative incidence of recurrent VTE was 2.9% in the low risk group, 4.8% in the intermediate risk group, and 8.2% in the high risk group [11]. Another prospective cohort study of 117 patients with symptomatic VTE and active cancer identified a similar modest 6-month c-statistic of 0.57 (95% CI, 0.37–0.77) [18]. The cumulative incidence of recurrent VTE in this study was 8.9% (95% CI, 2.8–19) in patients at low risk, and 11% (95% CI, 4.8–20) in those at high risk (SHR 1.3; 95% CI, 0.39–5.4) [18]. In contrast, den Exter and colleagues found a better predictive performance of the modified Ottawa score in a cohort of 419 cancer patients: the 6-month cumulative risk of recurrent VTE was 2.4% in patients at low risk, 8.8% in patients at intermediate risk, and 15.9% in those at high risk [8]. Likewise, Ahn et.al, evaluated the original dichotomous Ottawa score, and reported a cumulative risk of recurrent VTE of 13.2% in patients at low risk, and 22.4% in patients at high risk among 546 patients with active cancer and VTE [10].

The differences between the results of the present study and those of other validation studies might be caused by the higher overall incidence of recurrent VTE in these studies, which was up to 18.1% [8–11,18]. Several factors may explain this higher VTE recurrence rate, including a longer follow-up time [11], inclusion of patients with a short life expectancy [10], and the tendency of a higher VTE recurrence rate in cancer patients with symptomatic VTE [19]. The Ottawa risk score was derived from cohorts of cancer patients with symptomatic VTE and as such may not be relevant for patients with incidental VTE. Another potential explanation is that earlier studies included a large proportion of vitamin K antagonist recipients [8,10,11], while low-molecular-weight heparins and direct oral anticoagulants nowadays are the mainstay of treatment. Therefore, it is not sure whether our findings reflect a different performance of the score in cancer patients with incidental VTE compared to those with symptomatic VTE or merely a change in treatment of this condition in the last years.

Strengths of the present study include the large cohort of cancer patients with incidental PE who were prospectively followed for 12 months and the central adjudication of clinical outcomes. A competing risk approach was used for the analyses to account for the substantial mortality rate in this population.

A potential limitation of our study was the lack of data on the TNM stage, which was used as an item in the original score [7]. Using 'non-metastatic cancer' instead increases the risk of measurement bias possibly leading to more patients being falsely classified as low risk. However, the external validation cohorts presented in the original study as well as two other validation studies that used the same strategy were still able to reproduce the results of the original derivation cohort [7–9]. Sixty-three patients (9.1%) had a subsegmental PE as index event possibly leading to a lower event rate. The VTE recurrence rate in those with subsegmental PE, however, was similar as compared to more centrally located PE events (6.4% vs. 6.0%). A substantial proportion of recurrent VTE occurred after cessation of anticoagulant therapy, possibly affecting the performance of the Ottawa score, which was derived to predict recurrent VTE during anticoagulant treatment. However, when the analysis was restricted to recurrent VTE during anticoagulant therapy or within 7 days after discontinuation, the time dependent c-statistic was still modest: 0.51 at 6 months and 0.53 at 12 months. Likewise, the cumulative incidences of recurrent VTE and subdistribution hazard ratios between the risk groups while on-treatment were comparable with the primary analysis.

International guidelines suggest to treat patients with incidental VTE similar to those with symptomatic VTE, and to extend treatment as long as the cancer is active [5,6]. Adequate risk stratification for the risk of recurrence could enable individualized duration and intensity of anticoagulant treatment. This study showed that the modified Ottawa risk score should not be used for these purposes in cancer patients with incidental PE. Future studies should focus on identifying risk factors for anticoagulant-related bleeding and recurrent VTE in incidental VTE, which nowadays represents about 50% of all cancer-associated VTEs

[20].

Author contribution

All authors have made substantial contributions to (1) the conception and design of the study, acquisition of data, or analysis and interpretation of data, (2) drafting of the article and revising it critically for important intellectual content. All authors approved of the final version, and agree it to be submitted.

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Appendix A. Supplementary data

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