The Modified Ottawa Score and Clinical Events in Hospitalized Patients with Cancer-Associated Thrombosis from the Swiss VTE Registry

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Abstract

The modified Ottawa score (MOS) predicted venous thromboembolism (VTE) recurrence in a cohort of patients with cancer-associated thrombosis mainly managed on an outpatient basis. We aimed to assess the prognostic value of the MOS in hospitalized patients with cancer-associated thrombosis. In 383 hospitalized patients with cancer-associated VTE from the SWIss VTE Registry, 98 (25%) were classified as low risk, 175 (46%) as intermediate risk, and 110 (29%) as high risk for VTE recurrence based on the MOS. Clinical end points were recurrent VTE, fatal VTE, major bleeding, and overall mortality at 90 days. Overall, 179 (47%) patients were female, 172 (45%) had metastatic disease, and 72 (19%) prior VTE. The primary site of cancer was lung in 48 (13%) patients and breast in 43 (11%). According to the MOS, the rate of VTE recurrence was 4.1% for low, 6.3% intermediate, and 5.5% high risk ($p = 0.75$); the rate of fatal VTE was 0.8, 1.9, and 2.0% ($p = 0.69$); the rate of major bleeding was 3.1, 4.1, and 3.6% ($p = 0.92$); and the rate of death was 6.1, 12.0, and 28.2% ($p < 0.001$), respectively. None of the MOS items was associated with VTE recurrence: female gender hazard ratio (HR) 1.26 (95% confidence interval [CI], 0.53–2.96), lung cancer HR 1.17 (95% CI, 0.35–3.98), prior VTE HR 0.44 (95% CI, 0.10–1.91), breast cancer HR 0.83 (95% CI, 0.19–3.58), and absence of metastases HR 0.74 (95% CI, 0.31–1.74). In hospitalized patients with cancer-associated VTE, the MOS failed to predict VTE recurrence at 3 months but was associated with early mortality.

Keywords
- cancer
- mortality
- modified Ottawa score
- venous thromboembolism

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Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is one of the major causes of morbidity and mortality, and the second leading cause of death in cancer patients.[1,2] Patients with active cancer have a four- to sevenfold increased risk of developing VTE compared with patients without cancer.[1,2] In addition, the risk of VTE recurrence is significantly higher in cancer patients and varies according to the type, localization, and stage of cancer.[2]

Currently, patients with cancer and the first episode of VTE are generally treated with low-molecular-weight heparin (LMWH) as the drug of choice for 3 to 6 months.[3,4] This recommendation is based on the superiority of LMWH over vitamin K antagonist (VKA) in reducing the rate of VTE recurrence with a relative risk reduction of roughly 50%[5] and the paucity of data about the efficacy and safety of non-VKA oral anticoagulants (NOAC).[3,4] Treatment of cancer-associated VTE beyond 3 to 6 months of anticoagulation remains a challenge. Current guidelines and expert consensus suggest continuing anticoagulant therapy in patients with active cancer, preferably with LMWH.[3,4,6] However, this approach is not always feasible due to potential complications of the long-term use of LMWH (risk of bleeding or osteoporosis) and not easily acceptable by patients due to the burden of daily injections. A stratification of cancer patients according to their risk of VTE recurrence and the use of a different therapeutic strategy in low-risk (stopping anticoagulant therapy or using VKA or NOAC instead of LMWH) and high-risk (continuation of LMWH) patients may be an attractive alternative to the current approach.

Recently, Louzada et al proposed the Ottawa score, a clinical prediction rule that in its modified form allows classifying anticoagulated patients with active cancer and VTE in low-, intermediate-, and high-risk categories for VTE recurrence.[7] Reproducibility of the modified Ottawa score (MOS) has been confirmed in a Dutch study evaluating 419 patients[8] but not in a subanalysis from the CATCH study [Comparison of Acute Treatments in Cancer Haemostasis study] evaluating 900 patients.[9] To date, the MOS was validated in patients with cancer-associated VTE mainly managed on an outpatient basis, but it has not yet been evaluated in patients with cancer-associated thrombosis managed on an inpatient basis.

We aimed to assess the prognostic value of the MOS in hospitalized patients with cancer-associated VTE included in the Swiss VTE Registry (SWIVTER).

Patients and Methods

Patients

SWIVTER is a multicenter prospective registry, including consecutive inhospital or ambulatory patients, aged $\geq$ 18 years, with acute VTE confirmed by objective tests. The detailed SWIVTER methodology has been described elsewhere.[10]

In the present analysis, hospitalized patients enrolled in SWIVTER with concomitant cancer were separated in three groups according to the calculated MOS. The MOS was calculated as previously described.[7] 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 localized cancer without metastasis (stages 1 and 2 for solid tumors). Patients did not receive additional points for having a hematologic malignancy. Based on the MOS, the clinical probability 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 $\geq$ 1. The score was calculated retrospectively from the data collected upon hospital admission. SWIVTER did not issue any recommendations for diagnosis, treatment, or follow-up based on the calculated Ottawa score.

Clinical end points included recurrent VTE, fatal VTE, major bleeding, and overall mortality at 90 days. Recurrent VTE was defined as fatal or nonfatal objectively confirmed PE and/or DVT. Fatal VTE was defined as death following VTE in which VTE was considered a likely contributor to the fatal outcome. Major bleeding was defined in accordance with the International Society on Thrombosis and Haemostasis (ISTH) criteria as fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells.[11]

Data and Statistical Analysis

Continuous variables with a normal distribution were described as mean values with standard deviations (SDs), continuous variables with a skewed distribution as median values with interquartile ranges (IQRs), and discrete variables as frequencies and percentages. Group comparisons for continuous variables with a normal distribution were performed by *t*-test, for continuous variables with a skewed distribution by a rank-sum test, and for discrete variables by the chi-square or Fisher's exact test. The cumulative rates of clinical outcomes at 3 months were estimated with the Kaplan–Meier's method and compared by the use of a log-rank test. All reported *p*-values are two tailed. Data were analyzed using STATA 13 software (StataCorp LP).

Results

Patient Characteristics

Among 2,062 patients included in SWIVTER, 493 (24%) had cancer; of those, 383 (78%) were treated on an inpatient basis. Overall, the mean ± SD age was 63 ± 14 years, 179 (47%) patients were female, 172 (45%) had metastatic disease, and 72 (19%) had prior VTE. The primary site of cancer was genitourinary in 97 (25%) patients, gastrointestinal in 72 (19%), lung in 48 (13%), hematologic in 47 (12%), breast in 43 (11%), brain in 15 (4%), and other solid sites in 61 (16%). According to the MOS, 98 (25%) cancer patients were classified as low risk, 175 (46%) as intermediate risk, and 110 (29%) as high risk. Patient characteristics and comorbidities according to the risk category are summarized in ►**Table 1**. Congestive heart failure was associated with increasing risk

Table 1 Patient characteristics, chronic and acute comorbidities

	Low risk $N = 98$		Intermediate risk $N = 175$		High risk $N = 110$		Total $N = 383$		p
Demographics									
Age, mean y ± SD	70	13	67	15	68	11	68	14	0.46
Elderly (age ≥ 65 y), *n* (%)	67	68.4	104	59.4	76	69.1	247	64.5	0.16
Women, *n* (%)	15	15.3	83	47.4	81	73.6	179	46.7	< 0.001
Cancer									
Curative treatment plan, *n* (%)	85	86.7	106	60.6	42	38.2	233	60.8	< 0.001
Metastatic disease, *n* (%)	0	0.0	79	45.1	93	84.5	172	44.9	< 0.001
Life expectancy < 6 mo, *n* (%)	13	13.3	42	24.0	48	43.6	103	26.9	< 0.001
Chemotherapy, *n* (%)	15	15.3	56	32.0	27	24.5	98	25.6	< 0.001
Radiotherapy, *n* (%)	4	4.1	17	9.7	14	12.7	35	9.1	0.09
Chronic comorbidities									
Hypertension, *n* (%)	41	41.8	79	45.1	36	32.7	156	40.7	0.11
Prior VTE, *n* (%)	0	0.0	31	17.7	41	37.3	72	18.8	< 0.001
Congestive heart failure, *n* (%)	23	23.5	36	20.6	12	10.9	71	18.5	0.043
Diabetes mellitus, *n* (%)	18	18.4	33	18.9	20	18.2	71	18.5	0.99
Chronic lung disease, *n* (%)	12	12.2	24	13.7	24	21.8	60	15.7	0.10
Renal failure, *n* (%)	9	9.2	29	16.6	14	12.7	52	13.6	0.22
History of stroke/TIA, *n* (%)	10	10.2	10	5.7	10	9.1	30	7.8	0.35
Alcohol or drug abuse, *n* (%)	5	5.1	9	5.1	10	9.1	24	6.3	0.35
Hepatic impairment, *n* (%)	6	6.1	4	2.3	9	8.2	19	5.0	0.07
Hormone replacement, *n* (%)	1	1.0	10	5.7	3	2.7	14	3.7	0.12
Acute comorbidities within 30 d									
Prior hospitalization, *n* (%)	41	41.8	57	32.6	35	31.8	133	34.7	0.23
Acute infection/sepsis, *n* (%)	17	17.3	36	20.6	22	20.0	75	19.6	0.81
Bed rest > 3 d, *n* (%)	26	26.5	25	14.3	13	11.8	64	16.7	0.009
Surgery, *n* (%)	21	21.4	24	13.7	11	10.0	56	14.6	0.06
Acute respiratory failure, *n* (%)	12	12.2	18	10.3	12	10.9	42	11.0	0.88
Central venous catheter, *n* (%)	10	10.2	14	8.0	12	10.9	36	9.4	0.68
ICU admission, *n* (%)	14	14.3	8	4.6	6	5.5	28	7.3	0.009
Thrombocytopenia, *n* (%)	3	3.1	12	6.9	11	10.0	26	6.8	0.14
Bleeding requiring medical attention, *n* (%)	5	5.1	5	2.9	10	9.1	20	5.2	0.07
Acute heart failure, *n* (%)	10	10.2	2	1.1	1	0.9	13	3.4	< 0.001
Ischemic stroke or palsy, *n* (%)	4	4.1	4	2.3	5	4.5	13	3.4	0.54
Acute coronary syndrome, *n* (%)	2	2.0	8	4.6	2	1.8	12	3.1	0.33
Acute inflammatory/rheumatic disease, *n* (%)	4	4.1	5	2.9	3	2.7	12	3.1	0.82

Abbreviations: ICU, intensive care unit; SD, standard deviation; TIA, transient ischemic attack; VTE, venous thromboembolism.

in the MOS, while bed rest > 3 days, intensive care unit admission, and acute heart failure were associated with decreasing risk. VTE manifestation was similar in the three risk groups, including the diagnosis of symptomatic disease (87% in low risk, 86% in intermediate risk, and 89% in high risk; $p = 0.78$) and the diagnosis of PE (81, 73, and 68%, respectively; $p = 0.12$). In total, the median (IQR) duration of hospital stay was 10 (5–17) days; it was independent from the calculated risk in the MOS (10 [5–16] days in low risk, 8 [5–17] days in intermediate risk, and 11 [6–18] days in high risk; $p = 0.15$). The individual items of the MOS according to the risk category are shown in ►**Table 2**.

Table 2 Individual items of the modified Ottawa score

	Low risk $N = 98$		Intermediate risk $N = 175$		High risk $N = 110$		Total $N = 383$		p
Female sex, *n* (%)	15	15.3	83	47.4	81	73.6	179	46.7	< 0.001
Lung cancer, *n* (%)	0	0.0	7	4.0	41	37.3	48	12.5	< 0.001
Prior VTE, *n* (%)	0	0.0	31	17.7	41	37.3	72	18.8	< 0.001
Breast cancer, *n* (%)	15	15.3	25	14.3	3	2.7	43	11.2	0.004
Localized cancer, *n* (%)	98	100.0	96	54.9	17	15.5	211	55.1	< 0.001

Abbreviation: VTE, venous thromboembolism.

Treatment of Venous Thromboembolism

Overall, 242 (65%) hospitalized cancer patients received initial anticoagulation therapy with LMWH, 121 (33%) with unfractionated heparin, and 9 (2%) with NOAC. The long-term anticoagulation therapy with LMWH was used in 182 (49%) patients, with statistically significant difference between the three risk categories of the MOS (31, 50, and 66% for low, intermediate, and high risks, respectively; p <0.001). Treatment with LMWH for at least 3 months was administered in 115 (31%) patients, and it was associated with increasing risk in the MOS (16% in low risk, 31% in intermediate risk, and 46% in high risk; p <0.001).

Reperfusion therapy was used in 35 (9%) cancer patients, without any difference between the risk groups (10, 8, and 10% for low, intermediate, and high risks, respectively; $p = 0.78$).

Clinical Outcomes at 90 Days

The cumulative incidence of VTE recurrence at 90 days was 4.1% for low-risk patients, 6.3% for intermediate-risk patients, and 5.5% for high-risk patients ($p = 0.75$) (►**Fig. 1**). The rate of fatal VTE was 0.8% in low-risk patients, 1.9% in intermediate-risk patients, and 2.0% in high-risk patients ($p = 0.69$). At 90 days, overall mortality occurred in 6.1, 12.0, and 28.2% of low-, intermediate-, and high-risk groups, respectively (p <0.001) (►**Fig. 2**).

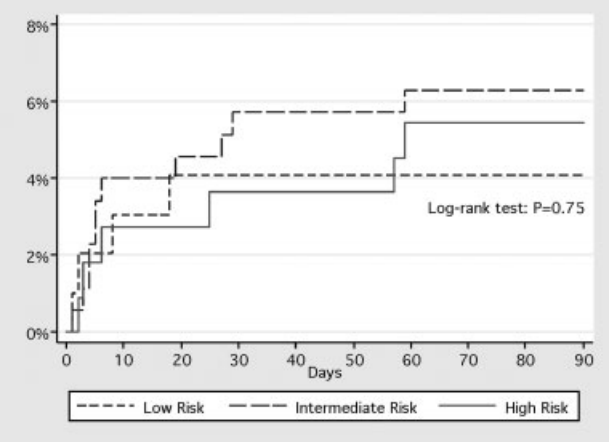

Fig. 1 Kaplan–Meier cumulative 90-day rates of recurrent VTE according to the modified Ottawa score in hospitalized patients with cancer.

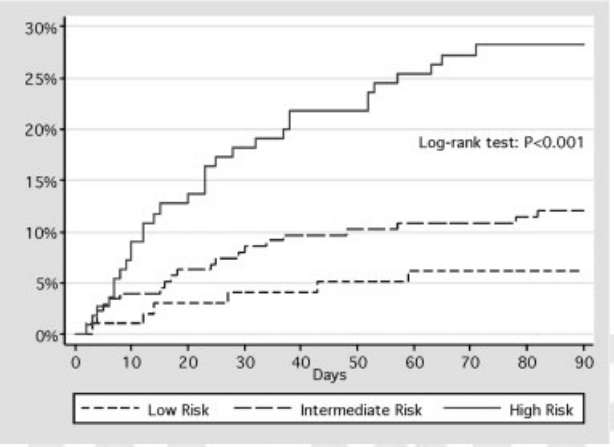

Fig. 2 Kaplan–Meier cumulative 90-day rates of overall mortality according to the modified Ottawa score in hospitalized patients with cancer.

The 90-day rate of bleeding requiring medical attention was 3.1% in low-risk patients, 7.4% in intermediate-risk patients, and 7.3% in high-risk patients ($p = 0.32$). Major bleeding at 90 days occurred in 3.1, 4.1, and 3.6% of in low-, intermediate-, and high-risk patients, respectively ($p = 0.92$).

At 90 days, none of the MOS items was associated with VTE recurrence: female gender hazard ratio (HR) 1.26 (95% confidence interval [CI], 0.53–2.96), lung cancer HR 1.17 (95% CI, 0.35–3.98), prior VTE HR 0.44 (95% CI, 0.10–1.91), breast cancer HR 0.83 (95% CI, 0.19–3.58), and absence of metastases HR 0.74 (95% CI, 0.31–1.74).

After adjustment for the use of LMWH for at least 3 months, neither the MOS (HR, 1.17; 95% CI, 0.65–2.12; $p = 0.60$) nor any of the MOS items predicted VTE recurrence at 90 days.

Discussion

In hospitalized patients with cancer-associated VTE from the SWIVTER, the MOS failed to predict VTE recurrence at 3 months. Moreover, none of the individual score items was associated with the occurrence of recurrent VTE. In contrast, the score was associated with 90-day overall mortality.

Our findings are consistent with results reported by Khorana et al[9] and Ahn et al[12] that were not able to confirm the validity of the modified and original Ottawa score for the prediction of VTE recurrence, respectively. The rates of recurrent VTE observed in SWIVTER (4.1% for low risk, 6.3% for intermediate risk, and 5.5% for high risk) differ from those reported in the validation sample by Louzada et al[7] (5.1, 9.9, and 15.8%, respectively), den Exter et al[8] (2.4, 8.8, and 15.9%, respectively), and Astruc et al[13] (2.6, 8.6, and 24.9%, respectively). Specifically, the occurrence of VTE recurrence in the high-risk group does not discriminate from the low- and intermediate-risk groups of the MOS in our cohort, similarly to the findings observed by Khorana et al[9] (3.4, 9.7, and 8.2%, respectively).

To the best of our knowledge, the present study is the first validation of the MOS in hospitalized patients with cancer-associated VTE. To date, the score was validated in patients with cancer-associated thrombosis mainly managed on an outpatient basis. Importantly, the Registro Informatizado de Enfermedad TromboEmbólica (RIETE) registry has explicitly shown that those who developed VTE as inpatients had a significantly higher incidence of fatal PE, overall death, and major bleeding than outpatients.[14] It is, therefore, not surprising that the MOS predicted death rather than recurrent VTE in the present analysis.

In general, the demographics and characteristics of many patients were similar across the various validation studies on the Ottawa score. The proportion of female gender was comparable in our analysis and validation cohorts by Louzada et al[7] and den Exter et al[8] (47 vs. 52 and 47%), and the same was true for the primary site of cancer: gastrointestinal (19 vs. 22 and 19%), lung (13 vs. 13 and 15%), hematologic (12 vs. 11 and 16%), and breast (11 vs. 17 and 8%), respectively. However, patients in our analysis were older than those in validation studies by Louzada et al[7] and den Exter et al[8] (68 vs. 63 and 60 years), and more often had prior VTE (19 vs. 9 and 12%), respectively.

On the contrary, our study differs from the previous validation studies in several aspects. First, patients with cancer-associated VTE managed on an inpatient basis were included in our analysis, whereas those mainly managed on an outpatient basis were enrolled in the prior validation studies. Often hospitalization is deemed to be a marker of disease progression or severity. Indeed, in the present study almost half of the patients in the high-risk group had life expectancy below 6 months. In contrast, the original validation study by Louzada et al[7] included patients with extended life expectancy. Second, the cumulative incidence of VTE recurrence was assessed at 90 days in SWIVTER and at 180 days in the validation studies by Louzada et al,[7] den Exter et al,[8] and Astruc et al.[13] In these studies, some patients may have discontinued or switched LMWH to VKA after the first 3 months, thus possibly increasing the risk of recurrent VTE. Third, only about half of the patients received LMWH for long-term anticoagulation in our study. The higher use of long-term LMWH in high-risk versus low- and intermediate-risk patients may have led to a bias against the MOS performance. Of interest, outpatient therapy was the strongest factor associated with the use of LMWH for at least 3 months in the multivariate analysis of the entire SWIVTER cohort.[10]

The present analysis is the first one to reveal that the MOS was predictive of early mortality. The very high 3-month mortality rate of 28% in the high-risk group is mainly explained by advanced cancer because 85% patients had metastatic cancer and almost half had a life expectancy of less than 6 months at the time of VTE diagnosis. In addition, more than one-third of the patients had lung cancer.

Our findings are hypothesis generating and require validation in further management and outcomes research. At present, the potential impact of our findings on the treatment strategy is unclear. In a systematic literature review on the long-term anticoagulation treatment of VTE in patients with cancer,[5] LMWH compared with VKA reduced VTE recurrence but not mortality. The ongoing trials evaluating the efficacy and safety of NOACs versus conventional anticoagulation in cancer patients with VTE[15–17] may offer additional insights whether or not emerging therapies impact on mortality.

The strategy to risk stratify patients with cancer-associated VTE remains a priority allowing for better-tailored treatment improving clinical outcomes while optimizing resources. Recent exploratory studies suggested that other parameters currently not reflected in the Ottawa score may be associated with VTE recurrence. Trujillo-Santos et al[18] showed that patients aged < 65 years with diagnosis of cancer within 3 months and clinically overt PE were at high risk for recurrent VTE. Recently, Khorana et al[9] proposed venous compression by tumor mass or adenopathy and diagnosis of hepatobiliary cancer as predictors of VTE recurrence. Nevertheless, we were surprised by our finding that none of the individual items of the MOS was associated with recurrent VTE.

The present SWIVTER analysis has limitations. First, we cannot rule out that several fatal VTEs were missed because autopsy was not routinely performed. Second, we cannot rule out that several nonfatal VTE events were missed because SWIVTER did not mandate standardized diagnostic work up in patients with symptoms or signs of VTE recurrence. Third, the Ottawa score was originally validated to predict 6-month VTE recurrence, whereas SWIVTER had only 3-month follow-up. Finally, SWIVTER was performed in Switzerland and the results may not apply to other countries. However, due to multicenter patient enrollment from large university hospitals, large- and middle-sized cantonal hospitals, and smaller regional hospitals across the country, involvement of departments of general internal medicine and divisions of angiology, and absence of exclusion criteria, we believe that the study population in SWIVTER was representative for hospitalized patients with cancer-associated VTE.

In conclusion, the MOS failed to predict VTE recurrence at 3 months but was associated with early mortality in hospitalized patients with cancer-associated VTE. Our finding requires validation by further research, including larger prospective management studies. The availability of validated risk stratification scores may contribute to improvement in long-term treatment of cancer-associated VTE.

Conflict of Interest

Dr. Spirk is an employee of Sanofi-Aventis (Suisse) SA, Vernier, Switzerland.

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