Clinical prediction scores for venous thromboembolism in patients with a hematological malignancy

Frits Mulder, MD, PhD
Nick van Es, MD, PhD
Department of Vascular Medicine, Amsterdam University Medical Center, Amsterdam, The Netherlands
n.vanes@amsterdamumc.nl

Introduction
Venous thromboembolism (VTE) is a common complication in patients with hematological malignancy with an overall incidence of approximately 3.5% per 100 person years(1). The risk of VTE varies substantially across different types of hematological malignancy, and also depends on cancer treatment, presence of a central venous catheter, and cancer stage(2). International guidelines recommend routine thromboprophylaxis in patients with multiple myeloma treated with immunomodulatory chemotherapy(3,4), but not in those with other hematological malignancies. Several risk scores have been developed to identify cancer patients at high risk of VTE in whom thromboprophylaxis may be justified, but only a few were specifically evaluated in patients with a hematological malignancy. This review aims to provide an overview of the performance and potential clinical utility of the currently available risk scores for cancer-associated VTE in patients with a hematological malignancy.

Khorana score
The most widely used risk assessment tool for cancer-associated VTE is the Khorana score, which is now endorsed by several guidelines(5,6). This risk score aims to identify ambulatory patients with solid cancer or lymphoma at high risk of VTE prior to cancer therapy based on five clinical and laboratory parameters: primary tumor site (e.g. +1 point for lymphoma), platelet count of 350 x 10^9/L or more (+1 point), hemoglobin concentration of less than 10 g/dL and/or use of erythropoiesis-stimulating agents (+1 point), leukocyte count of more than 11 x 10^9/L (+1 point), and body mass index of 35 kg/m^2 or more (+1 point)(7). The score was derived in a prospective cohort of 2,701 cancer patients, of whom 12% patients had lymphoma. In the internal validation cohort of 1,365 patients, the observed 3-month VTE risk was 6.7% in patients with a high risk score (≥3 points) compared to 1.5% in patients with a low or intermediate risk score (0-1 points), corresponding to a relative risk (RR) of 4.5 (95% confidence interval [CI] 2.2-9.3).

Keywords: venous thromboembolism, hematological malignancy, prediction.
Results were not reported separately for lymphoma patients, which limits the generalizability of the findings for this particular group. In addition, the score was not intended to be used in patients with other types of hematological malignancies. In the past 3 years, several studies addressed these issues by evaluating the performance of the Khorana score in patients with various hematological malignancies, as summarized in Table 1. Taken together, these external validation studies show that the relative risk of VTE in patients with a hematological malignancy and a high risk Khorana score is lower (1.2 to 2.4) than reported in the original derivation study. This was confirmed in a recent systematic review and meta-analysis showing a 1.5-fold higher risk of VTE in patients with a hematological malignancy and a Khorana score ≤2 than in those with a Khorana score ≥3\(^{[8]}\). Whether this is due to differences in case-mix, study design, or follow-up duration, or reflects a lower performance in patients with a hematological malignancy in general remains unknown. Another concern is the low proportion of patients classified as high risk, ranging between 5 and 15%, which, in combination with the modest relative risks, limits the clinical utility of the score in selecting patients for thromboprophylaxis. The reported positive predictive values (7 to 19%) may be high enough to justify thromboprophylaxis, but differences in follow-up duration and types of included cancers make it difficult to translate these findings to clinical practice (Table 1). The score has not been validated in patients with acute leukemia, because these patients often have abnormal blood counts. Whether extending the Khorana score with D-dimer and soluble P-selectin levels, as proposed by Ay and colleagues, improves risk stratification in lymphoma patients is unknown\(^{[9]}\).

Table 1. Studies evaluating risk scores for thrombosis in patients with a hematological malignancy

<table>
<thead>
<tr>
<th>First author</th>
<th>Number of patients</th>
<th>Type</th>
<th>Follow-up duration</th>
<th>Outcome</th>
<th>Overall incidence (%)</th>
<th>Patients in high risk group (%)</th>
<th>Positive predictive value (%)</th>
<th>RR for high vs lower risk patients (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khorana 2008 (derivation cohort)(^{[7]})</td>
<td>2701*</td>
<td>Lymphoma</td>
<td>Median 73 days</td>
<td>VTE</td>
<td>60 (2.2)*</td>
<td>340 (12.6)*</td>
<td>7.1*</td>
<td>4.6 (2.8-7.7)*</td>
</tr>
<tr>
<td>Khorana 2008 (validation cohort)</td>
<td>1365†</td>
<td>Lymphoma</td>
<td>Median 73 days</td>
<td>VTE</td>
<td>28 (2.1)†</td>
<td>149 (10.9)†</td>
<td>6.7†</td>
<td>4.5 (2.1-9.6)†</td>
</tr>
<tr>
<td>Lim 2015(^{[17]})</td>
<td>322</td>
<td>DLBCL</td>
<td>Median 42 months</td>
<td>VTE</td>
<td>34 (10.6)</td>
<td>16 (4.9)</td>
<td>18.8</td>
<td>1.9 (0.6-5.4)</td>
</tr>
<tr>
<td>Antic 2016 (cohort 1)(^{[18]})</td>
<td>1236</td>
<td>NHL, HL, CLL, SLL</td>
<td>NR</td>
<td>ATE, VTE</td>
<td>65 (5.3)</td>
<td>NR</td>
<td>14.8</td>
<td>NR</td>
</tr>
<tr>
<td>Antic 2016 (cohort 2)(^{[18]})</td>
<td>584</td>
<td>NHL, HL, CLL, SLL</td>
<td>NR</td>
<td>ATE, VTE</td>
<td>34 (5.8)</td>
<td>NR</td>
<td>14.8</td>
<td>NR</td>
</tr>
<tr>
<td>Rupa-Matyseck 2017(^{[19]})</td>
<td>428</td>
<td>DLBCL, HL</td>
<td>Median 37 months</td>
<td>VTE</td>
<td>64 (15)</td>
<td>64 (15)</td>
<td>17</td>
<td>1.2 (0.7-2.1)</td>
</tr>
<tr>
<td>Santi 2017(^{[20]})</td>
<td>1189</td>
<td>DLBCL, FL INFL, MCL</td>
<td>6 months</td>
<td>VTE</td>
<td>41 (3.4)</td>
<td>141 (11.9)</td>
<td>7.1</td>
<td>2.4 (1.2-4.8)</td>
</tr>
</tbody>
</table>
**ThroLy score**

The ThroLy score was developed by Antic and colleagues for predicting venous and arterial thrombotic events in ambulatory lymphoma patients. The score is composed of seven clinical and laboratory variables and was derived in 1,236 patients with lymphoma or chronic lymphocytic leukemia receiving chemotherapy. In the internal validation cohort of 584 patients, the risk of arterial or venous thromboembolism was 29% in patients with an intermediate or high risk score (≥2 points) compared to 2.4% in those with a low risk score (0-1 points). The c-statistic of the score was 0.86. However, important information needed to fully appreciate the score’s performance, such as follow up-duration and proportion of patients classified as being at risk, were unfortunately not reported. Both venous and arterial thromboembolic events, including superficial thrombophlebitis, were part of the outcome, which limits the use of the score when deciding about primary VTE prevention. Although the ThroLy score appears promising, it needs to be validated in external patient cohorts before it can be implemented in clinical practice.

**IPSET-thrombosis score**

The International Prognostic Score for Essential Thrombocythemia (IPSET) score was developed to

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### ThroLy score

| Antic 2016 (derivation cohort) | 1236 | NHL, HL, CLL, SLL | NR | ATE, VTE | 65 (5.3) | NR | 25.1 | NR |
| Antic 2016 (validation cohort) | 584 | NHL, HL, CLL, SLL | NR | ATE, VTE | 34 (5.8) | NR | 28.9 | NR |

### IPSET thrombosis score

| Barbui 2012 (derivation cohort) | 535 | ET | Median 6.5 years | ATE, VTE | 59 (11) | 63 (12) | 17.5 | 1.7 (0.9-3.1) |
| Barbui 2012 (internal validation cohort) | 356 | ET | Median 6.1 years | ATE, VTE | 44 (12.4) | 48 (14) | 22.9 | 2.1 (1.2-3.9) |
| Barbui 2012 (external validation cohort) | 329 | ET | Median 5.0 years | ATE, VTE | 31 (9.4) | 164 (50) | 12.8 | 2.1 (1.0-4.4) |
| Fu 2014 | 746 | ET | Median 49 months | ATE, VTE | 77 (10.3) | 221 (29.6) | 19.5 | 3.0 (2.0-4.6) |
| Sevindik 2015 | 112 | ET | Median 4.1 years | ATE, VTE | 38 (33.9) | 45 (40.2) | 62.2 | 4.2 (2.3-7.7) |
| Navarro 2016 | 44 | ET | NR | ATE, VTE | 19 (43.2) | 24 (54.6) | 25.0 | 15.0 (2.2-102.8) |

* Of the total study group, 12% had lymphoma and 88% a solid cancer.
† Of the total study group, 14% had lymphoma and 86% a solid cancer

Abbreviations: ATE, arterial thromboembolism; CLL, chronic lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; ET, essential thrombocythemia; FL, follicular lymphoma; HL, Hodgkin’s lymphoma; INFL, indolent non-follicular lymphoma; NHL, non-Hodgkin lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; NR; not reported; RR; relative risk; SLL, small lymphocytic lymphoma; VTE, venous thromboembolism.
predict arterial or venous thrombotic events in patients with essential thrombocythemia (ET). The score is based on four variables: age 60 years or older (+1 point), cardiovascular risk factors (+1 point), previous thrombosis (+2 points), and JAK2V617F mutation (+2 points). The risk of arterial or venous thrombotic event in the high risk group (≥3 points) ranged between 13 and 23% in the original derivation, internal validation, and external validation cohorts. Several external validation studies confirmed the discriminatory performance of the IPSET score with reported relative risks of thrombosis between 3.0 and 15 in high risk patients (Table 1). The group that introduced the IPSET-score subsequently proposed a ‘practice-relevant revision’ by stratifying patients into four groups based on age, previous thrombosis, and JAK2V617F mutation. Although the score appeared to perform well in an external validation study, its ability to improved risk-adapted prophylaxis needs to be confirmed in prospective studies.

**Thromboprophylaxis risk assessment tool for multiple myeloma**

A VTE risk assessment tool was developed by the International Multiple myeloma Working Group (IMWG) for patients with multiple myeloma receiving immunomodulatory drugs. The tool consists of a list of 17 patient-, myeloma-, and treatment-specific risk factors. If no or any one of the risk factors is present in a patient receiving thalidomide or lenalidomide, aspirin once daily is recommended. If two or more risk factors are present, a prophylactic dose of low-molecular-weight heparin or warfarin targeted at an INR of 2 to 3 is recommended. The IMWG risk score is based on expert opinion without any validation studies, and should therefore not be regarded a firm guideline.

**Future perspectives**

The Khorana score has now been evaluated in several studies of patients with hematological malignancies, but results are not unambiguous. Given the uncertainty, clinicians should be cautious to use the score to select patients for thromboprophylaxis. The lymphoma-specific ThroLy score and ET-specific (revised) IPSET-scores are promising, but need additional external validation before they can be used in clinical practice. Future studies need to focus either on validating existing scores in different settings or on developing new models that more accurately select patients with a high short-term risk of VTE. Ideally, scores should then be used to guide risk-adapted thromboprophylaxis in randomized trials to confirm their performance and clinical benefit, as was previously done for patients with solid cancer.

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**Bibliografía**


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