Scores to Identify Occult Cancer in Venous Thromboembolism: Do They Work?

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The optimal management of venous thromboembolism (VTE) has long been a clinical challenge.[1] Unprovoked VTE may be the earliest sign of cancer, and this association has been long recognized.[2,3] Indeed, up to 10% of patients with unprovoked VTE will receive a diagnosis of cancer in the year after their diagnosis of VTE.[4]

Therefore, clinicians and scientists have long advocated systematic testing of asymptomatic individuals (i.e. screening) for pre-clinical occult malignancy. Subjecting patients to an extensive diagnostic workup could alter their clinical course: an earlier cancer diagnosis might potentially lead to earlier and more effective treatment and would also affect anticoagulation choice. However, routine screening for occult cancer after unprovoked VTE is not supported by current evidence. The Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism (SOME) trial randomized patients with unprovoked VTE to a limited screening strategy involving standard age- and sex-specific screening or to an extensive strategy that added computed tomography of the abdomen and pelvis.[5] Among 854 patients, the primary outcome of the study (the number of cancers 'missed' at the initial screening but diagnosed by the end of the 1-year follow-up period) was 0.93% in the limited screening group and 1.18% in the extensive screening group.

Since a sub-group of high-risk patients could potentially benefit from a more extensive occult cancer screening strategy, investigators have developed risk scores that might provide a basis for effective screening and preventive strategies. For example, Jara-Palomares et al identified 6 independent predictors (RIETE score) assessed at the time of VTE presentation of occult cancer in a 24-month follow-up period: male sex, age $>$ 70 years, chronic lung disease, anaemia (haemoglobin levels $<$ 13 g/dL for men and $<$ 12 g/dL for women), elevated platelet count ($\geq$ 350,000 $\times$ 1,000/mm^3), prior VTE and recent surgery.[6] For each patient, the score assigned 2 points each for the presence of age $>$ 70 years and anaemia, and 1 point each for the presence of male sex, chronic lung disease and raised platelet count; and 2 negative points for the presence of recent surgery. Patients with a total score of $\leq$ 2 were assigned to the low-risk category, and those with a total score of $\geq$ 3 points to the high-risk category. Six percent (95% confidence interval [CI], 5.1–6.6%) of the low-risk patients versus 12% (95% CI, 10.4–13.5%) of the high-risk patients were diagnosed with cancer during follow-up.[6] Ihaddadene et al performed a posthoc analysis of the SOME trial and found that age $\geq$ 60 years (hazard ratio [HR], 3.1; 95% CI, 1.4–6.9; $p = 0.005$), previous provoked VTE (HR, 3.2; 95% CI, 1.2–8.62; $p = 0.022$) and current smoker status (HR, 2.8; 95% CI, 1.2–6.3; $p = 0.014$) were associated with occult cancer detection (SOME score).[7]

To show that a prognostic model is valuable, it is not sufficient to show that it successfully predicts outcome in the initial development data. We need evidence that the model performs well for other groups of patients.[8] It is important to check the proportion of patients classified by the rule in the different prognostic groups, as well as its accuracy and calibration. The validation cohort should represent an unselected group of patients with a wide spectrum of disease severity, and the predictors for the rule should be collected blinded from the final outcome.

In the previous issue of *Thrombosis and Haemostasis*, Kraaijpoel and a team of renowned clinical scientists

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performed a posthoc analysis of the Hokusai-VTE trial to evaluate the performance of the RIETE and SOME scores for the occurrence of subsequent occult cancer in patients with acute VTE.[9] A total of 8,032 patients were included in the analysis. The incidence of occult cancer was 1.8% in patients with unprovoked VTE (5,359 patients, 67%), and 2.1% in those with provoked VTE (2,673 patients, 33%). The RIETE score classified 19% of patients as having a 'high risk' of occult cancer and the SOME score 16%. In patients classified as 'high risk', the cumulative incidence of cancer diagnosis during follow-up was 2.9% (95% CI, 2.1–3.9%) for the RIETE score and 2.7% (95% CI, 1.9–3.7%) for the SOME score, corresponding to HRs of 1.8 (95% CI, 1.3–2.5) and 1.5 (95% CI, 1.04–2.2), respectively. The *C*-statistics of the RIETE and SOME scores were 0.62 (95% CI, 0.57–0.66) and 0.59 (95% CI, 0.55–0.62), respectively.

Various factors might explain the relatively poor predictive capability of the two models assessed in this study. The models' predictions might not be reproducible because of deficiencies in the modelling methods used in the study to derive the model. Poor performance could also arise from differences between the setting of patients in the new and derivation samples. Randomized controlled trials (RCTs) are currently the best approach to evaluate the effectiveness of therapies while accounting for the effects of unmeasured confounders and selection bias by indication. However, there is reasonable concern about inadequate representativeness of RCTs. In a recent study by the RIETE registry on the real-life use of direct oral anticoagulants in patients with VTE, 19% met at least one exclusion criterion for the trials where the indication was established.[10] The higher incidence of occult cancer in the sub-group of patients with provoked VTE (compared with the sub-group of patients with unprovoked VTE) might suggest that a non-representative group of patients were enrolled in the Hokusai-VTE trial.

Based on the results of the Kraaijpoel et al study, the value of these scores is questionable. Other factors such as presence of extensive VTE (including bilateral deep vein thrombosis) have recently shown promise,[11] whereas more traditional cancer risk factors such as longstanding history of smoking, alcohol overuse, history of radiation and family history of early cancer may warrant further assessment. In addition, cancer-specific biomarkers might improve the discriminative performance of these risk scores and require further validation (ClinicalTrials.gov; NCT02739867). The final step would involve assessing the impact of its use on practice patterns, outcomes of care and costs.[12] Until these score are available, a limited screening strategy involving standard age- and sex-appropriate screening is advisable.

Conflict of Interest
None.

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