JACC: ASIA VOL. 1, NO. 2, 2021

EDITORIAL COMMENT

Risk Assessment for Cancer-Associated VTE

Diversifying the Evidence Base*

Alok A. Khorana, MD

Why is risk assessment and prediction of cancer-associated venous thromboembolism (VTE) so important? First, VTE, which comprises deep venous thrombosis, pulmonary embolism, and visceral vein thrombosis, is highly prevalent in people with cancer, and its incidence is rising (1). Second, VTE is highly consequential for patients: it is associated with short- and long-term mortality, emergency room visits, and hospitalizations, and potential interruption or delay of cancer therapy and its treatment is associated with risk of major bleeding (2,3). Third, VTE leads to substantial consumption of health care resources (4). Fourth, despite paradigm shifts in treatment of cancer away from chemotherapy toward immunotherapy and targeted therapy, VTE remains a known complication of both older and newer treatment regimens for cancer (1,5). Most frustrating, however, the risk of VTE in people with cancer is not equally distributed but varies substantially between cancer subpopulations, and even in the same patient, over time. Hence, it is essential to accurately identify patients at risk for cancer-associated VTE.

This need has become more urgent with emerging data demonstrating the safety and efficacy of prophylactic anticoagulation in patients with cancer at higher risk of VTE (6). In 2008, my colleagues and I published a risk tool to identify patients with cancer at risk of VTE using baseline clinical and laboratory variables before the start of a new systemic therapy regimen (7). This risk tool, subsequently referred to in the literature as the Khorana score, has since been validated in several prospective and retrospective cohort studies, totaling more than 50,000 patients in published reports (8,9). The Khorana score formed the basis of 2 randomized trials of prophylaxis with direct oral anticoagulants (DOACs) that focused on inclusion of patients at higher risk (score ≥2) (10,11). A recent meta-analysis of 6 trials of either DOACs or low molecular weight heparin found that prophylaxis significantly reduced VTE risk in intermediate- to high-risk (score ≥2) (RR: 0.51; 95% confidence interval [CI]: 0.34-0.67), intermediate-risk (score = 2) (RR: 0.58; 95% CI: 0.36-0.83), and high-risk patients (score ≥3) (RR: 0.45; 95% CI: 0.28-0.67); the numbers needed to treat were 25 (intermediate to high risk), 34 (intermediate risk), and 17 (high risk), respectively. As a result of these findings, all major guidelines currently recommend using the Khorana score for risk assessment for cancer-associated VTE and for selection of patients with score ≥2 for thromboprophylaxis (12,13).

A major limitation of the development and validation of this score, however, has been the lack of diversity in study populations. VTE rates can vary by race and ethnicity; for instance, Asian American patients appear to be at lower risk and Black patients are at greatest risk for cancer-associated VTE (14,15). Body mass index (BMI), 1 of 5 components of the Khorana score, is known to be lower in Asian populations. However, Black and Asian patients comprised only a small minority of patients in development and validation study populations as well as randomized trials (eg, <2% of patients in CASSINI [Rivaroxaban for Preventing Venous Thromboembolism in High-Risk Ambulatory Patients with Cancer] were Asian and <5% were Black [10]).

*Editorials published in *JACC: Asia* reflect the views of the authors and do not necessarily represent the views of *JACC: Asia* or the American College of Cardiology.

From the Taussig Cancer Institute and Case Comprehensive Cancer Center, Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, Ohio, USA.

The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2021.07.007

It is in this context that the paper in the current issue of *JACC: Asia* by Akasaka-Kihari et al. (16) validating the Khorana score in a Japanese population assumes substantial importance. The authors analyzed the utility of the Khorana score in more than 27,000 patients from a single institution participating in a multicenter prospective Kumamoto Prefecture-wide registry. Notably, the authors modified the original score by altering the cutoff of BMI from 35 kg/m^2 in the original study to 25 kg/m^2 (aligning with the definition of obesity for an Asian population and consistent with a BMI cutoff in a prior study of Japanese patients with lung cancer [17]). Overall rate of VTE was 5.3% but varied substantially by Khorana score, ranging from 1.7% in low-risk patients to 11% in high-risk patients. Similar to other reports in Western (primarily White populations), the Khorana score was also an independent predictor of mortality in this study.

There are, of course, several limitations to this study. This was a single-institution study, but its prospective nature and substantial sample size make up for this limitation. The population included surgical patients, whereas the Khorana score was specifically developed and validated in the context of initiation of systemic therapy; it is unclear how much better or worse the score would have performed if surgical settings were excluded. The authors propose a lower score cutoff (≥1) to identify Japanese patients at higher risk of VTE but this needs validation, as acknowledged in the paper.

Overall, however, the authors are to be congratulated on confirming the validity of the Khorana score in the Japanese population with a rational modification of the original score. These findings are important for knowledge translation and implementation of thromboprophylaxis protocols in the context of recent guideline updates if we are to reduce the public health burden of cancer-associated VTE for people who already suffer from the overwhelming burden of cancer and its treatment. Finally, modifying and validating a previously developed risk score in diverse populations is important for future risk assessment approaches. For instance, emerging data suggest that somatic mutations and genetic alterations may be an important predictor of VTE in cancer (18,19). If such alterations are included in future risk scores, it will be important to study them in diverse populations in an accelerated fashion. Akasaka-Kihari et al (16) have done the field a service by providing a template for future such studies that will doubtless be necessary as the science of risk prediction continues to rapidly evolve.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Khorana has received research support from the Sondra and Stephen Hardis Endowed Chair in Oncology Research and the Consortium Linking Oncology to Thrombosis funded by the National Heart, Lung and Blood Institute (5U01 HL14340202); and has reported personal fees and nonfinancial support from Janssen, Bayer, Bristol Myers Squibb, Sanofi, Pfizer; personal fees from Anthos, Medscape; and grants (to institution) from Merck, Array, Bristol Myers Squibb, and Leap, all outside the submitted work.

ADDRESS FOR CORRESPONDENCE: Dr Alok A. Khorana, Taussig Cancer Institute, Cleveland Clinic Foundation, 10201 Carnegie Avenue, CA60, Cleveland, Ohio 44195, USA. E-mail: Khorana@ccf.org.

REFERENCES

1. Mulder FI, Horvath-Puho E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. *Blood*. 2021;137:1959–1969.

2. Mulder FI, Bosch FTM, Young AM, et al. Direct oral anticoagulants for cancer-associated venous thromboembolism: a systematic review and meta-analysis. *Blood*. 2020;136:1433–1441.

3. Chen YW, Wang MJ, Khorana AA. Prevalence of venous thromboembolism diagnosed in emergency department visits by cancer patients and associated healthcare resource utilization in the United States. *Am J Hematol*. Published online May 23, 2018. https://doi.org/10.1002/ajh.25148

4. Khorana AA, Kuderer NM, McCrae K, et al. Healthcare costs of patients with cancer stratified by Khorana score risk levels. *J Med Econ*. 2021;24:866–873.

5. Roopkumar J, Swaidani S, Kim AS, et al. Increased incidence of venous thromboembolism with cancer immunotherapy. *Med (N Y)*. 2021;2:423–434.

6. Bosch FTM, Mulder FI, Kamphuisen PW, et al. Primary thromboprophylaxis in ambulatory cancer patients with a high Khorana score: a systematic review and meta-analysis. *Blood Adv*. 2020;4:5215–5225.

7. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111:4902–4907.

8. Mulder FI, Candeloro M, Kamphuisen PW, et al. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. *Haematologica*. 2019;104:1277–1287.

9. Khorana AA, Kuderer NM, McCrae K, et al. Cancer associated thrombosis and mortality in patients with cancer stratified by Khorana score risk levels. *Cancer Med*. 2020;9:8062–8073.

10. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. *N Engl J Med*. 2019;380:720–728.

11. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. *N Engl J Med*. 2019;380:711–719.

12. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol*. 2020;38:496–520.

13. Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. *Blood Adv*. 2021;5:927–974.

14. Addo-Tabiri NO, Chudasama R, Vasudeva R, et al. Black patients experience highest rates of cancer-associated venous thromboembolism. *Am J Clin Oncol*. 2020;43:94–100.

15. Alcalay A, Wun T, Khatri V, et al. Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. *J Clin Oncol*. 2006;24:1112–1118.

16. Akasaka-Kihara F, Sueta D, Ishii M, et al. Validation of the Khorana venous thromboembolism risk score in Japanese cancer patients. *JACC: Asia*. 2021;1:259–270.

17. Hiraide M, Shiga T, Minowa Y, et al. Identification of risk factors for venous thromboembolism and evaluation of Khorana venous thromboembolism risk assessment in Japanese lung cancer patients. *J Cardiol*. 2020;75:110–114.

18. Dunbar A, Bolton KL, Devlin SM, et al. Genomic profiling identifies somatic mutations predicting thromboembolic risk in patients with solid tumors. *Blood*. 2021;137:2103–2113.

19. Roopkumar J, Poudel SK, Gervaso L, et al. Risk of thromboembolism in patients with ALK- and EGFR-mutant lung cancer: a cohort study. *J Thromb Haemost*. 2021;19:822–829.

KEY WORDS malignancy, prevention, risk score, thromboembolism