Modeling Complexity: The Case of Cancer-Related Venous Thromboembolism

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Personalized medicine—broadly defined as tailoring medical treatment to individual patient and/or tumor characteristics—is increasingly gaining relevance in cancer medicine. For instance, genomic predictors such as RAS status (wild-type or mutant) are mandatory to determine choice of therapy in people with colorectal cancer (antiepidermal growth factor receptor antibody for wild-type). Similarly, a 21-gene recurrence score is used to quantify distant recurrence risk and chemotherapy benefit in breast cancer patients. Personalizing clinical decisions become more complex when multiple variables need to be taken into account. As data availability expands, prognostic and predictive multivariable modeling is increasingly being used to forecast individual outcomes and—using simplified tools based on these multivariable models—to facilitate decision-making. This approach has become so common that grocery store chains, for instance, use multivariate modeling to identify customers who have become pregnant—occasionally, before the customer's family is even aware!

Can such models be successful in highly dynamic states? One important test case is cancer-associated thrombosis—the occurrence of deep vein thrombosis or pulmonary embolism in patients with active cancer. Venous thromboembolism (VTE) in cancer patients is highly consequential commonly leading to morbidity, emergency room visits, hospitalization, and, above all, mortality.[1] The pathophysiology of thrombosis in this setting is both multifactorial (to name a few factors: type of cancer, stage, chemotherapy, surgery, placement of catheter) and dynamic (treatments, patient functional status, acute illnesses, and tumor burden can occur or alter rapidly over periods of days to weeks). How can all these variables be harnessed to better predict risk of VTE in cancer? In 2008, my colleagues and I developed and validated a risk assessment tool based on a multivariable model to identify patients at low, intermediate, or high risk for VTE.[2] In the past decade, this score has been validated in multiple settings and evaluated in over 35,000 patients.[3] Since the original publication, multiple other models have also been developed and evaluated (reviewed in Khorana[4]). In general, however, for most of these models the positive predictive value is low, and improvements to risk assessment are necessary. This issue has taken on special relevance recently given that risk assessment can now be utilized to select patients for thromboprophylaxis.[5,6]

In this issue, Carmona-Bayonas et al raise important issues with current approaches to risk modeling and identify alternatives.[7] The authors highlight the fact that VTE in cancer is a time-dependent variable, that is, it occurs over the course of several months to years in patients with ongoing, active malignancy which can bias modeling approaches. The authors hypothesized that using alternative approaches such as multistate and flexible models can lead to a better understanding of this illness. They examined this hypothesis in a registry of patients with advanced gastric cancer which included a prespecified collection of thrombotic endpoints. Their findings focused on two different aspects of cancer-associated VTE. First, they explored the effect of developing VTE on mortality and found a lessening of association which is not suitably understood using traditional modeling approaches (i.e., hazard ratios); VTE that took place later in the course had a more pronounced prognostic effect. It should be noted that such findings, using multistate modeling, were previously reported by the Vienna group in this journal.[1] These investigators similarly found that VTE events during follow-up were associated with a threefold increase in the risk of death, adjusted for stage and VTE that occurred later during follow-up exerted a stronger impact on the risk of death (hazard ratio for VTE occurrence 1 year after baseline vs. at baseline =2.30, 95% confidence interval: 1.28–4.15).

Second, Carmona-Bayonas et al explored predictors of cancer-associated VTE and found that two specific predictors (Khorana score and tumor burden) had a more pronounced

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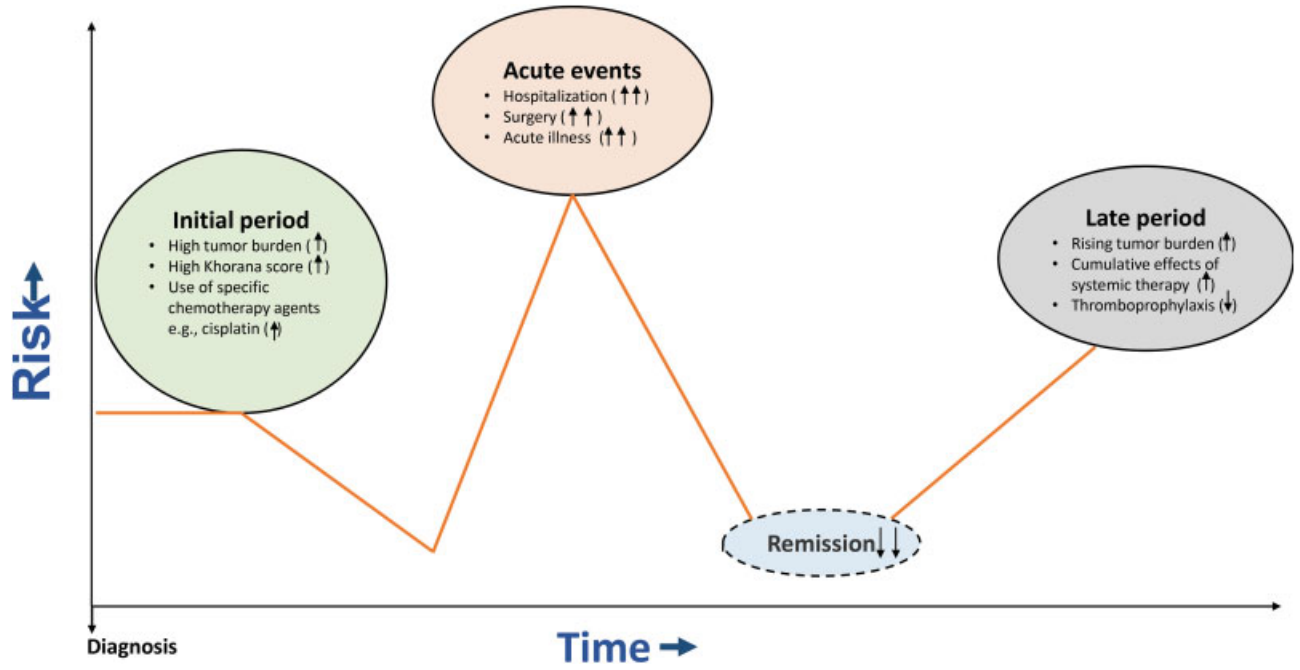

Fig. 1 An illustration representing dynamic changes in risk factors for cancer-associated thrombosis over time.

association with early VTE. This is not altogether surprising, since in our original publication, we had intended the use of this score primarily to predict VTE in the first 3 months after initiating a new systemic therapy regimen. Prediction further in the course of the illness requires a reevaluation of risk and the findings by Carmona-Bayonas et al confirm this (►**Fig. 1**).

The study certainly has limitations as acknowledged by the authors including focus on a single site/stage of cancer (advanced gastric). However, the authors intend this as a proof-of-concept study and, together with the original paper on multistate modeling in this disease by Posch et al,[1] have in fact proven the concept that flexible, multistate models are promising methodologies to better assess risk of cancer-associated VTE as well as its impact on mortality.

A larger issue with predictive or prognostic models is that investigators tend to focus on evaluating performance based on baseline-derived parameters and statistical tests, such as sensitivity, specificity, positive/negative predictive values, and area under the receiver operating characteristic curve, However, as a recent commentary points out, a test of far greater importance to patients is often left out: *will classification from the model result in a favorable change in the individual patient's care?*[8] Risk prediction models also have to account for the dynamic nature of risk, where reliance on baseline assessment alone may be insufficient given that over time patients get older, tumor burden can increase, acute events such as hospitalization or medical illnesses can occur, and incident risk factors can be acquired as evident by literature in other conditions, such as atrial fibrillation (►**Fig. 1**).[9]

Indeed, there are test measures such as decision curve analysis that can help interpret study findings in context of clinical utility.[10] This patient-centered question also opens up issues of real-world applicability and effectiveness if flexible or dynamic approaches to risk modeling are to be considered in clinical settings. Current applications—at time of initial diagnosis or initial systemic therapy—are relatively straightforward to implement.[11] But future applications with a dynamic score requires much more complicated logistics. How will clinicians, currently unable or unwilling to even provide basic education about VTE to cancer patients,[12] make determinations about a change in risk of VTE in an individual patient? How can electronic medical records or health system approaches be altered to identify an acute, dire increase in risk of VTE for an individual patient, communicate this change in classification to the treating physician, who can then have an informed discussion with the patient regarding risk/benefit of thromboprophylaxis? These questions also need to be considered as we look forward to an era of improving methodologies for risk prediction in cancer medicine.

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Conflict of Interest
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