

Predictive Biomarkers of Thromboembolic Events in Cancer

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Editorial

Cancer-associated thrombosis is characterized by several pathophysiological mechanisms, evidencing that tumour biology and coagulation processes are closely linked. Tumor cells interact via multiple pathways with platelets and thereby promote metastasis formation, angiogenesis, protection from immune surveillance, tumor growth, and invasion [1].

Today, the association of cancer and thrombosis is well-recognized in clinical practice. Several epidemiological studies have shown that venous thromboembolism (VTE) is a common complication of cancer and its therapy. The risk of VTE in cancer patients is 4-7 fold higher compared to individuals without cancer. Up to 20% of cancer patients develop VTE, which is recognized as one of the leading causes of death in these patients [2].

However, the cancer population is heterogeneous in terms of thrombosis risk. Rates of VTE widely differ in subgroups of cancer patients and depend on the presence of various patient-, tumor-, and treatment-related risk factors [3].

For instance, age, obesity, medical comorbidities, and immobilization add to the risk of VTE in the general population as well as in cancer patients. The primary site of cancer and the presence of metastatic disease are among the most important risk factors for cancer-associated thrombosis, with highest VTE rates observed in patients with brain, pancreatic and gastric cancer. Also patients with haematologic malignancies, particularly those with lymphoma and multiple myeloma, have relatively high rates of VTE [4-7].

Furthermore, cancer-related treatments including chemotherapy and antiangiogenic agents, hormonal therapy, surgery, and erythropoiesis-stimulating agents predispose to VTE [8-10].

Thus, Predictive biomarkers could aid in identifying patients at high risk for VTE. An ideal biomarker is easily measurable, standardized, and has high sensitivity, specificity, and predictive value for subsequent thrombosis. It also remains a strong predictor over time, even in a patient receiving antithrombotic agents.

A number of laboratory parameters or biomarkers, which are predictive of cancer-associated VTE, have been recently identified. A high platelet count or a high leukocyte counts have been shown to significantly increase the VTE risk [11].

Furthermore, biomarkers reflecting activation of the blood clotting system, such as D-dimer or sP-selectin, or an increase in the

inflammatory potential, such as CRP, are elevated in cancer patients and may be predictive of both primary and recurrent VTE [12].

Presently, D-dimer seems to be one of the most promising candidates to gain a role for prediction of VTE in cancer patients, with the aim to identify patients who in all probability would benefit most from thrombosis prophylaxis [3].

The Vienna Cancer and Thrombosis Study (CATS) has contributed to new findings, which may help identify patients at high risk of developing VTE, by means of biomarkers (such as D-dimer, prothrombin fragment 1+2, soluble P-selectin, platelet count, coagulation factor VIII activity, thrombin generation potential, etc.) [13].

However, there are limitations for some of these biomarkers for various reasons: (1) they are dependent on factors other than the tumor itself, eg, additional inflammation due to infection, coagulation activation by surgery, or other invasive procedures; and (2) the sensitivity and specificity of single biomarkers are low. The specificity is considerably improved by combining clinical factors with biomarkers and creating scores [12].

Therefore, a novel and promising approach to stratify cancer patients according to their risk of VTE is the use of risk scoring models.

Several groups have developed risk assessment models to predict chemotherapy-associated thrombosis in ambulatory cancer patients that incorporate demographic, tumor, host, treatment, and laboratory data. Recently, Khorana and colleagues stratified patients undergoing chemotherapy for cancer into three risk categories based on 5 clinical and laboratory parameters: primary cancer site, pre-chemotherapy platelet count $\geq 350 \times 10^9/L$, hemoglobin < 10 g/dL or use of erythropoietin-stimulating agents, leukocyte count $> 11 \times 10^9/L$, and BMI ≥ 35 kg/m² [14].

However, this risk scoring system has not yet been independently validated in other studies. Further development of risk stratification models should explore the usefulness of incorporating other biomarkers, such as P-selectin, CRP, factor VIII, prothrombin F 1+2, and TF-bearing microparticle levels, into VTE prediction models and expand the risk models to include patients with a cancer diagnosis who are not receiving chemotherapy.

To elucidate the usefulness of these parameters for assessment of VTE risk and for routine primary thromboprophylaxis in preventing VTE based on haemostatic biomarkers, future prospective, interventional and randomized-controlled trials are needed.

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