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SEED Haemostasis

The clinical utility of D-dimer testing in cancer patients

What is D-dimer?

An extrinsic or intrinsic trigger of the coagulation cascade concludes in the generation of thrombin, which then converts fibrinogen into fibrin monomers comprised of a so-called 'E' domain and two 'D' domains. The fibrin monomers are covalently crosslinked and consequently stabilised via thrombin-activated factor XIII to form an insoluble and stable fibrin clot. This cross linkage irreversibly binds the D domains of two adjacent fibrin molecules to each other. In health, the process of clot formation is finely balanced with the simultaneous initiation of clot inhibition by natural anticoagulants such as antithrombin, activated protein C and clot breakdown, called fibrinolysis, to ensure the blood vessel lumen is not occluded. The process of fibrinolysis is mediated via the enzyme plasmin which can cleave fibrin monomer, cross-linked fibrin and fibrinogen into a heterogeneous mixture of fibrinogen degradation products (FDPs). The covalent bond formed between two D domains is, however, resistant to plasmin cleavage. FDPs containing 2 such D domains are referred to as D-dimer and originate exclusively from cross-linked fibrin (Fig. 1).

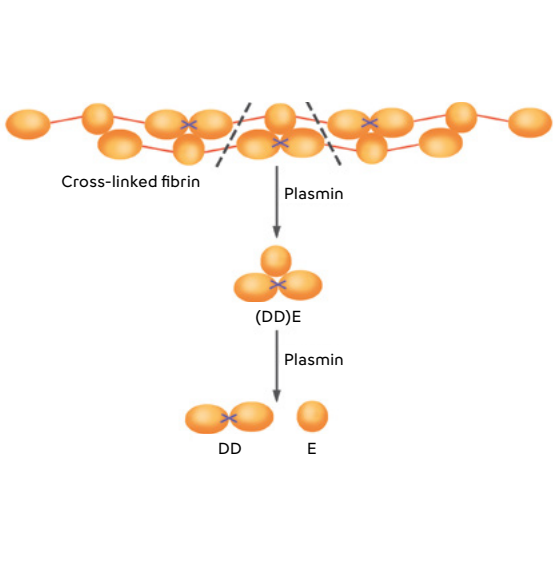

Fig. 1: Schematic representation of D-dimer formation

Although D-dimer is not one molecule or analyte but a mixture of closely related proteins from fibrin degradation, no international standard preparation is currently available for D-dimer(s), rendering it difficult to compare results of different D-dimer assays [1].

Why are D-dimers so important to test in cancer patients?

Cancer is a diverse group of potentially fatal diseases characterised by uncontrolled cell growth, which can manifest in any part of the body. Early detection and treatment are crucial for improving survival rates.

Cancer is also associated with an increased thromboembolic risk. After the cancer itself, venous thromboembolism (VTE) is the second most common cause of death in patients with an active cancer [2]. One in five cancer patients suffer from a thromboembolic event and one in five patients with VTE have cancer (Fig. 2).

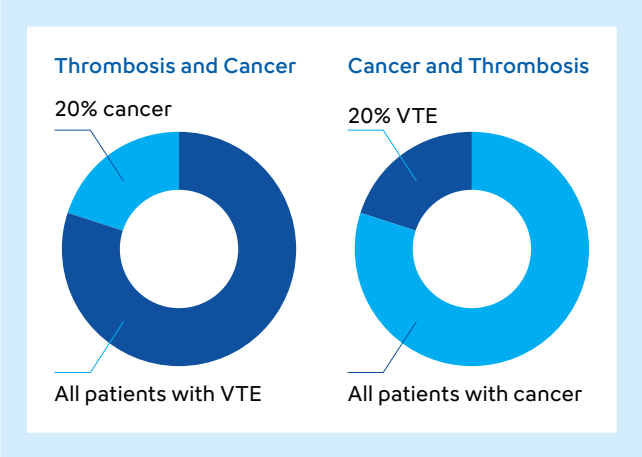

Fig. 2: Proportions of thrombosis in cancer and cancer in thrombosis (adapted from (2))

The association of cancer and thrombosis has been shown in many studies including different cancer types and sites [3, 4]. The type of cancer, including the site where the tumour grows, has a major impact on the thromboembolic risk profile, with cancers such pancreatic cancer or stomach cancer posing a very high thrombotic risk for patients. In addition to cancer type, many contributors to the VTE risk of cancer patients have been described, ranging from patient characteristics to tumour- and treatment-related risk factors (Fig. 3).

Anti-cancer treatments and therapies have evolved and improved survival rates dramatically in recent years, but they can carry a significant thrombotic risk burden as described, for instance, for check-point inhibitor therapy [5] and long known for chemotherapy [6]. Thus, cancer- and treatment-related thrombotic risks require constant assessment and management to avoid potentially life-threatening

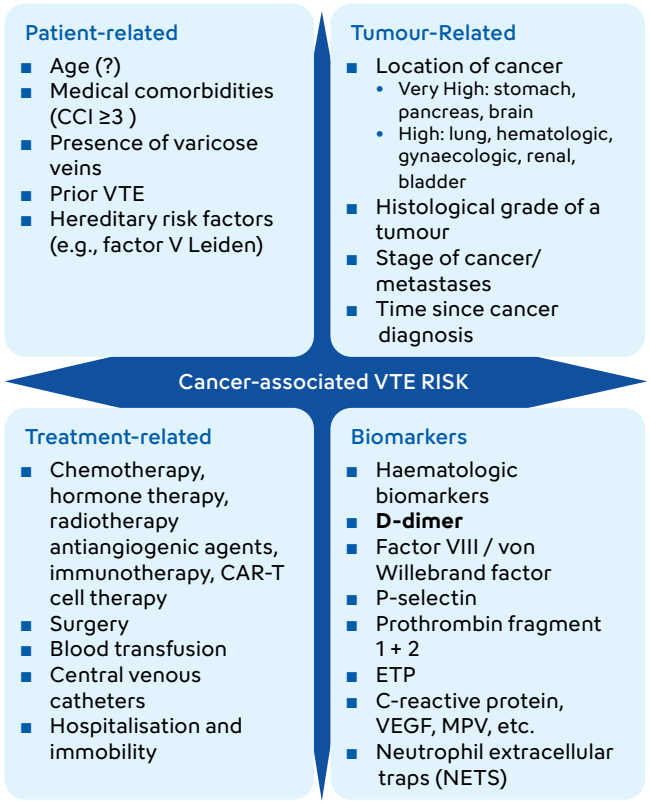

Fig. 3: Risk Factors and Predictors for VTE in Cancer Patients.
CAR-T cell = Chimeric Antigen Receptors-T cell,
TAT = Thrombin-Antithrombin Complex,
ETP = Endogenous Thrombin Potential,
VEGF = Vascular endothelial growth factor,
MPV = Mean Platelet Volume (adapted from (12) with updates)

complications following the diagnosis of the cancer and the subsequent therapy. Various laboratory biomarkers in patient plasma have been identified indicating coagulation activation, either preceding or accompanying a thrombotic event (see Fig. 3). Among those biomarkers, plasma D-dimer is the most reliable and accessible laboratory parameter. Table 1 summarises the association of D-dimer levels and thrombotic risk in prospective clinical studies [3]. Consequently, the thrombotic risk prediction model Vienna CATScore utilises plasma D-dimer levels to identify those cancer patients with the highest thrombotic risk requiring anti-thrombotic measures such as direct oral anticoagulation [4]. The Vienna CATScore uses tumour site and D-dimer as continuous variables to predict VTE risk. An app to calculate the Vienna CATScore and a detailed description of the score's formula are available online*.

*Scan to learn more about the Vienna CATScore

Table 1: D-dimer and the risk of cancer-associated thrombosis. FEU = Fibrin equivalent unit; DDU = D-dimer unit; HR = hazard ratio; sHR = subdistribution hazard ratio; OR = odds ratio. (adapted from (3) with modifications).

Ref	Type of cancer	No. of patients	Cut-off	Statistics	95% CI
Primary VTE risk					
[7]	Colorectal	176	>0.3 µg/mL DDU	HR 6.53	1.58–27.0
[8]	Mixed	124	>0.65 µg/mL FEU	HR 4.04	1.22–13.3
[9]	Mixed	821	≥1.44 µg/mL FEU	HR 1.8	1.0–3.2
[10]	Gynaecologic	267	>5 µg/mL FEU	OR 1.19	1.04–1.37
[11]	Lung	108	>1.50 µg/mL FEU	HR 11.0	2.62–46.2
[12]	Pancreatic	140	≥2.16 µg/mL FEU	HR 4.9	1.0–23.1
[13]	Mixed	946	Per 10 µg/m LFEU increase	sHR 1.31	1.00–1.73
Recurrent VTE risk					
[14]	Mixed	117	>4.0 µg/mL FEU	sHR 2.5*	0.76–7.9
[15]	Mixed	111	>0.60 µg/mL FEU >age × 0.01 µg/mL FEU	sHR 5.81 sHR 5.11	1.06–31.72 1.032–25.3

This prediction model and the older, well known Khorana Score [16] have recently been compared and validated in prospective clinical studies [17, 18]. While both models showed their efficacy in identifying patients with increased risk of VTE and both demonstrated their usefulness in clinical practice, the CATScore showed a better discriminatory capacity for VTE [17]. Therapeutic anticoagulation of patients identified with a high VTE risk resulted in a number needed to treat (NNT) of 13 at the time of inclusion in the study [18], meaning only 13 cancer patients need to be prophylactically anticoagulated to prevent 1 thrombotic event. An even lower NNT of 6 for primary thromboprophylaxis with a DOAC (Direct Oral Anticoagulant) was shown in a pot hoc analysis of the AVERT trial, if patients were stratified into high- and low-risk groups according to the CATScore [19]. The American Society of Hematology (ASH) provided guidance and recommendations on when and how to implement thromboprophylaxis in cancer patients with low-molecular weight heparins (LMWH), with DOACs being the anticoagulants recommended [20].

Take-home message

- In cancer patients, thrombosis is the second most common cause of death after the cancer itself.
- Plasma D-dimer is a key laboratory parameter for the assessment and stratification of the thrombotic risk in cancer patients.
- D-dimer included in risk prediction models such as the Vienna CATScore helps identify those cancer patients who may benefit most from therapeutic anticoagulation with LMWH or DOACs as recommended by current guidelines.

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