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REVIEW ARTICLE

Hemostasis and cancer: Impact of haemostatic biomarkers for the prediction of clinical outcomes in patients with cancer

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Abstract

Patients with cancer are characterized by a dysregulation of the hemostatic system and systemic hypercoagulability. Different components of the hemostatic system are involved in tumor-promoting mechanisms including primary tumor growth, cancer cell invasion, immune evasion, angiogenesis, and the metastatic process. Therefore, different degrees of systemic hemostatic activation in patients with cancer can reflect distinct underlying biological phenotypes of cancer and seem to correlate with cancer aggressiveness. Peripheral blood levels of hemostatic biomarkers, indicating the activation status of different parts of the hemostatic system including the coagulation cascade, fibrinolytic activity, platelet activation, or endothelial activation, can be used to reflect cancer-associated systemic hypercoagulability. Thereby, hemostatic biomarkers represent promising candidates to investigate as surrogate markers for underlying cancer activity and progression dynamics and therefore as biomarkers for the prediction of clinical outcomes in cancer patients. In the present review, we provide an up-to-date summary of available data on hemostatic biomarkers for prognostication of overall survival and prediction of therapy response in patients with cancer, including specific oncologic treatment settings for potential clinical application. We provide a thorough discussion on potential clinical implementation and current limitations and highlight the most promising emerging biomarkers that might be used to contribute to risk-stratified, personalized oncologic decision making in the future.

KEYWORDS
biomarkers, cancer, clinical decision-making, hemostasis, prognosis

1 | INTRODUCTION

Cancer is characterized by a dysregulation of different biological systems that are physiologically involved in hemostasis.[1] Systemic hypercoagulability and risk of thromboembolic complications in patients with cancer have been well characterized and the concept of bidirectional pathways between cancer and the blood coagulation system was established.[2,3]

Current epidemiologic estimates suggest a relative increase in risk of venous thromboembolism (VTE) by a factor of 9 compared with individuals without cancer.[4] However, VTE risk is heterogenous and largely depends on the underlying individual prothrombotic risk profiles of patients.[5] In part, VTE risk is influenced by underlying patient-specific risk factors including age, sex, and comorbidities, and is further affected by cancer-specific treatments.[2,3,6] Importantly, risk of cancer-associated VTE largely depends on the

underlying type and stage of cancer, with VTE rates of up to 20% in patients with high-risk tumors such as pancreatic or gastric cancer, indicating distinct tumor specific mechanisms for cancer-associated hypercoagulability.[7] Further, VTE diagnosis is an independent predictor for decreased survival in cancer patients, suggesting overt thrombotic manifestations in patients with cancer as a reflection of more aggressive underlying cancer phenotypes, disease progression, and treatment failure.[8–11]

Different pathophysiological pathways were identified in the interplay between cancer and different components of the hemostatic system. The overexpression of procoagulant molecules, most prominently tissue factor (TF) as the main activator of coagulation *in vivo*, was found in different cancers.[12–15] Interestingly, specific genetic alterations in malignant cells were linked to TF overexpression.[14,16,17] The prothrombotic effect is further enhanced locally by the expression of TF on tumoral stroma and vascular endothelial cells, and systemically by the release of TF-bearing extracellular vesicles (EV-TF).[18–25] In addition, impaired fibrinolysis via tumoral overexpression of plasminogen-activator-inhibitor-1 (PAI-1), the main inhibitor of fibrin degradation, contributes to a procoagulant phenotype of the tumor microenvironment.[26,27] In return, activation of the coagulation cascade promotes the development and progression of cancer. Activated coagulation proteases including thrombin directly activate cellular receptors that are overexpressed in many cancers (proteinase activated receptors), triggering intracellular signaling cascades involved in tumor growth, invasion, and angiogenesis.[13,28–33] Further, local coagulation activity in the tumor niche leads to a tumor-promoting micro-environment supporting growth, invasion, neo-angiogenesis, and immune evasion.[34–36] Additionally, platelets play a vital role in the pathophysiology of cancer.[1,37,38] Platelets are activated in the context of cancer either directly via receptor mediated mechanisms, or indirectly via the release of platelet-activating molecules.[39] Platelets play a crucial role in promoting pro-tumoral mechanisms by supporting a microenvironment of proliferation and angiogenesis via the release of cytokines and growth factors. Further, platelets facilitate metastasis by mechanical shielding and supporting immune evasion of circulating tumor cells.[40–44] Indirectly, cancer-associated hypercoagulability is further influenced by a tight biological link between cancer, inflammation, and the hemostatic system. Cancer-induced local and systemic inflammatory mechanisms activate hemostasis via pro-inflammatory cytokines and neutrophil extracellular traps.[1,45–48]

Synoptically, the close bidirectional crosstalk between cancer and the hemostatic system promotes hypercoagulability in cancer patients. Consequently, different degrees of systemic hemostatic activation can reflect underlying biology of tumors. Thus, markers of systemic hypercoagulability and hemostatic activation might be suitable candidates as surrogate parameters for the clinical aggressiveness of cancers. In the present review, we comprehensively summarize available data on hemostatic biomarkers for the prediction of clinical outcomes in patients with cancer, including survival and therapy response. We critically review the potential for clinical application of different biomarkers in different oncologic treatment settings and give an outlook on potential future directions of hemostatic biomarkers in oncologic risk prediction (Figure 1).

1.1 | Hemostatic biomarkers

Hemostatic biomarkers, defined as biomarkers that are either directly involved in or indirectly reflect the activation status of the hemostatic system, are a heterogeneous group of biological molecules, cells, or parameters from laboratory assays that evaluate hemostatic processes. These biomarkers reflect different physiological compartments of the hemostatic system, including blood coagulation, fibrinolysis, platelet activation, or endothelial cell activation. Many of these biomarkers are well characterized parameters with a low financial and logistical burden of clinical application. In Table 1, we provide a concise overview on the type and physiological role of frequently evaluated hemostatic biomarkers in patients with cancer.

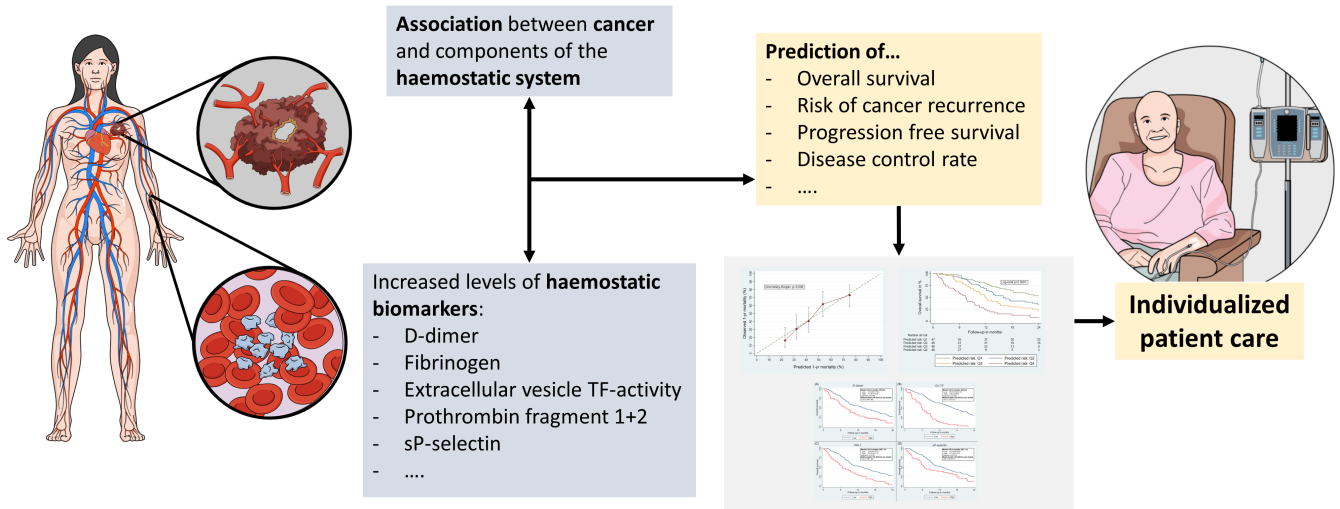

FIGURE 1 Schematic illustration of potential clinical application of hemostatic biomarkers in patients with cancer.

TABLE 1 Overview of selected frequently investigated hemostatic biomarkers in patients with cancer

Biomarker	Physiological role	Significance in cancer
D-Dimer	Product of plasmin-mediated fibrin degradation Reflects systemic coagulation and fibrinolytic activity Used in diagnostic workup for VTE	Increased levels compared with healthy controls Used for personalized prediction of cancer-associated VTE Broadly evaluated for survival and treatment response prediction in various cancer types
Fibrinogen	Substrate for fibrin generation Acute phase protein: increased in response to physiologic stimuli including inflammation, tissue injury, or malignancy	Inconsistent data on predictive utility for cancer-associated VTE Widely investigated for prediction of survival and therapy response in cancer
TF-expression and EV-TF	Direct initiation of the coagulation cascade Overexpression of TF in many cancers Shedding of EV-TF in the circulation by cancer cells	TF expression and levels of EV-TF linked to biological attributed of tumors (vascular invasion, tumor grade) EV-TF linked to survival outcomes, especially in pancreatic cancer
F1 + 2	Shed from prothrombin upon thrombin generation Reflects intravascular coagulation activity	Levels associated with VTE risk in cancer Surrogate marker for cancer-associated hypercoagulability Infrequently investigated as prognostic biomarker in cancer
sP-selectin	Released from platelets and endothelial cells upon activation (major source: platelets)	Higher levels associated with increased risk of VTE and ATE in cancer Infrequently investigated as prognostic biomarker in cancer
PAI-1	Main inhibitor of fibrinolysis *in vivo* Overexpressed levels in different cancers	Elevated levels linked to hypercoagulability in cancer PAI-1 expression linked to biological features of cancers Investigated for prediction of survival and therapy response in different cancers
TFPI	Physiologic inhibitor of the coagulation cascade	Suggested tumor suppressive effect in *in vitro* studies Selected studies on tumoral TFPI-expression and peripheral plasma levels for oncologic prediction
TGA	*In vitro* assay, reflecting systemic hypercoagulability Frequently evaluated parameters include ETP and peak TG	Predictive utility for cancer-associated VTE Association with oncologic outcomes was investigated in several studies, especially in breast cancer
FVIII	Reflects activation state of coagulation cascade Indicates systemic hypercoagulability	Elevated FVIII levels observed in cancer patients Predictive utility for cancer-associated VTE Limited data on prediction of survival and therapy response in cancer
TAT	Accumulates in response to increased thrombin generation Indicates systemic coagulation activation	Limited data on prediction of survival and therapy response in cancer
ATIII	Inhibitory protein of the coagulation cascade	Limited data on prediction of survival and therapy response in cancer
Protein C	Inhibitory protein of the coagulation cascade	Limited data on prediction of survival and therapy response in cancer

Abbreviations: ATIII, antithrombin III; ATE, arterial thromboembolic events; EV-TF, extracellular vesicle tissue-factor activity; ETP, endogenous thrombin potential; F1 + 2, prothrombin fragment 1 + 2; FVIII, coagulation factor VIII activity; PAI-1, plasminogen activator inhibitor 1; peak-TG, peak thrombin generation; sP-selectin, soluble P-selectin; TAT, thrombin antithrombin complex; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TGA, thrombin generation assay; VTE, venous thromboembolism.

2 | HEMOSTATIC BIOMARKERS FOR THE PREDICTION OF SURVIVAL AND THERAPY RESPONSE IN CANCER PATIENTS

Emerging evidence support the prognostic and predictive utility of specific hemostatic biomarkers in different therapeutic settings in patient with various cancers. The clinical range of potential application for hemostatic biomarkers in cancer patients is divers and include (1) prognostication of overall survival (OS), (2) prediction or monitoring of disease recurrence risk after curative surgery (disease-free survival [DFS]), and (3) the prediction or monitoring of response to systemic anticancer therapies, indicated by outcome parameters including progression-free survival (PFS) or radiological disease control rate (DCR). Other clinical applications of hemostatic biomarkers including the prediction of primary cancer risk or prediction of cancer-associated VTE are not discussed in the present review.[49] In the following section, we review available literature that report data on the use of hemostatic biomarkers for the prediction of survival and therapy response outcomes in patients with cancer. Table 2 provides an overview of selected studies reporting hemostatic biomarkers for prognostication of overall survival and prediction of therapy response outcomes in patients with cancer.

TABLE 2 Selected studies on hemostatic biomarkers for prognosis and prediction of therapy response in patients with cancer

Cancer type	Biomarkers	Study	Design	Setting	*n*
Different cancers (15% lung, 13% breast, 13% brain, 11% lower GI, 11% prostate)	*D-dimer*	Ay et al.[50]	PCS	Newly diagnosed or recurrent cancer	1178
Different solid tumors, heterogenous types, stage, settings	*D-dimer*	Li et al.[51]	Meta-analysis	Heterogeneous settings	13001
Lung cancer	*D-dimer, sP-sel., FVIII, F1 + 2, FGEN, TGA*	Moik et al.[63]	PCS	Advanced disease, before systemic treatment	277
Lung cancer	*D-dimer*	Ma et al.[62]	Meta-analysis	Heterogeneous settings	11 studies, 1625 pts.
Lung cancer	*FGEN*	Zhong et al.[66]	Meta-analysis	Heterogeneous settings	16 studies, 6881 pts.
Gastrointestinal cancers	*D-dimer, FGEN*	Lin et al.[71]	Meta-analysis	Heterogeneous settings	37 studies, 12359 pts.
Colorectal cancer	*D-dimer*	Oya et al.[68]	RCS	Resected CRC	93
Colorectal cancer	*D-dimer, FVIII, sP-sel., F1 + 2, FGEN, TGA*	Moik et al.[74]	PCS	Metastatic CRC before systemic chemotherapy	99
Colorectal cancer	*FGEN*	Sun et al.[70]	RCS	Resected CRC	1869
Colorectal cancer	*sP-selectin*	Ferroni et al.[69]	RCS	Primary ($n = 149$) or metastatic ($n = 31$) CRC	181
Pancreatic cancer	*D-dimer, FGEN*	Zhang et al.[78]	RCS	Resected pancreatic cancer	282
Pancreatic cancer	*EV-TF*	Thaler et al.[23]	PCS	Newly diagnosed or recurrent cancer	60
Pancreatobiliary cancer	*EV-TF*	Bharthuar et al.[80]	RCS	Newly diagnosed	118 (pancreatic: $n = 80$, biliary: $n = 34$)
Pancreatic cancer	*D-dimer, sP-selectin, FGEN, F1 + 2, Peak TG, ETP*	Moik et al.[81]	PCS	Newly diagnosed or recurrent cancer	145
Breast cancer	*Thrombin generation potential*	Giaccherini et al.[89]	PCS	Surgically resected pts. at high risk for recurrence	522
Ovarian cancer	*D-dimer*	Wu et al.[92]	Meta-analysis	Heterogeneous	15 studies, 1437 pts.
Gastric cancer	*FGEN*	Yu et al.[95]	RCS	Patients undergoing gastrectomy	1196
Gastric cancer	*D-dimer*	Liu et al.[96]	RCS	Patients undergoing gastrectomy	247

Abbreviations: CRC, colorectal cancer; DCR, disease control rate; DD, D-dimer; DFS, disease-free survival; ETP, endogenous thrombin generation potential; EV-TF, extracellular vesicle tissue factor activity; FGEN, fibrinogen; F1 + 2, prothrombin fragment 1 & 2; FGEN, fibrinogen; FVIII, coagulation factor VIII; GI, gastrointestinal; HR, hazard ratio; n.s., no significant association; OR, odds ratio; OS, overall survival; PCS, prospective cohort study; PFS, progression-free survival; pts., patients; RCS, retrospective cohort study; sP-sel., soluble P-selectin; TGA, thrombin generation assay.

Biomarker timepoint	Biomarker cutoff	OS	PFS	Other Outcomes
At study inclusion, pretherapeutic	Continuous (per double increase)	Adj. HR: 1.5 (1.4–1.6)	-	-
Pretreatment	High vs. low (different cutoffs)	Pooled HR: 1.90 (1.63–2.20)	HR: 1.46 (1.22–1.76)	DFS: HR 2.02 (1.56–2.62)
Pretreatment	Continuous (per double increase)	Adj. HR: DD: 1.50 [1.29–1.75] sP-s.: 1.42 [1.09–1.83] FVIII: 1.46 [1.08–1.98] FGEN, F1 + 2, TGA: n.s.	Adj. HR: DD: 1.34 [1.16–1.53] F1 + 2.: 1.22 [1.04–1.44]	Adj. OR for DCR: DD: 0.73 [0.52–1.04] F1 + 2: 0.71 [0.50–1.02]
Heterogeneous	Different cut-offs	Pooled HR: 2.06 [1.64–2.58]	-	-
Heterogeneous,	Different cutoffs, subanalysis for cutoff 400 mg/dL	Pooled HR: 1.38 (1.22–1.55)	Pooled HR: 1.29 (1.01–1.65)	-
Heterogeneous	Different cutoffs	Pooled HR: DD: 2.06 (1.79–2.38) FGEN: 1.60 (1.44–1.79)	-	-
Presurgical	Continuous (log-scale)	HR 2.3 (1.3–4.1)	-	-
Pretherapeutic	Continuous (per double increase)	Adj. HR: DD 1.40 (1.18–1.65), FVIII: 2.06 (1.28–3.30), sP-sel.: 1.55 (1.07–2.24), F1 + 2: 1.64 (1.10–2.46) TGA, FGEN: n.s.	-	OR for DCR: FVIII: 0.23 (0.09–0.62), F1 + 2: 0.36 (0.16–0.82)
Presurgical	Cutoff: 364 mg/dL	Adj. HR (low vs high): 0.78 (0.63–0.96)	-	-
Presurgical or pretherapeutic	Cutoff: 75 ng/mL (mean + 2 SD)	HR CRC-specific mortality: 3.44 (1.24–9.51)	HR for recurrence in primary CRC: 2.22 (1.14–4.32)	-
Presurgical	D-dimer: 0.53 mg/L FGEN: 331 mg/dl	Adj. HR: DD: 1.36 (1.02–1.80), FGEN: 1.60 (1.20–3.14)	-	-
Pretreatment	Continuous (per double)	Adj. HR: 1.8 (1.4–2.3)	-	-
Pretreatment	Cutoff: EV-TF activity > = 2.5 pg/ml	Adj. HR: 2.5 (1.4–4.5)	-	-
Pretherapeutic	Continuous (per double)	Adj. HR: DD: 1.33 (1.08–1.66), PAI-1: 1.25 (1.08–1.45), sP-sel.: 1.42 (1.00–2.01) FGEN, peak TG, ETP: n.s.	Adj. HR: DD: 1.29 (1.03–1.61)	Adj. OR for DCR: 0.61 (0.38–0.99)
Before systemic chemotherapy	Continuous	-	-	HR for early disease recurrence: 1.001 (1.001–1.002)
Heterogeneous	Different cutoffs	pooled HR: 1.32 [0.90–1.95]; restricted to $n > 100$: HR 1.80 [1.28–2.52]	-	-
Presurgical	4.0 g/L	Adj. HR: 1.36 [1.14–1.62]	-	-
Presurgical	1.465 µg/ml	Adj. HR: 2.28 [1.36–3.81]	-	-

2.1 | Tumor-type agnostic

Several hemostatic biomarkers were evaluated for their prognostic utility in general cohorts of cancer patients with heterogeneous tumor types. Most prominently, different studies focused on levels of D-dimer as biomarkers of interest. The association between D-dimer and all-cause mortality was studied in a large prospective observational cohort study including patients with newly diagnosed or recurrent cancer (n = 1178; most frequent tumor types: lung, 15%; breast, 13%; brain, 13%; lower gastrointestinal, 11%). Higher levels of D-dimer measured at study inclusion were independently prognostic for increased mortality risk beyond tumor type, age, sex, and VTE occurrence during follow-up (hazard ratio [HR] per double: 1.5; [95% confidence interval [CI] 1.4–1.6]), with a 1-year-OS according to elevating D-dimer quartiles of 88%, 82%, 66%, and 53%, and corresponding 2-year-OS of 78%, 66%, 50%, and 30%, respectively.[50]

In 2018, a large-scale meta-analysis was published, pooling data from 49 studies reporting on the association between D-dimer levels and cancer outcomes, including a total of 13001 patients. Included studies varied substantially in tumor types, treatment settings, study design, and biomarker cutoffs. However, an overall association between higher D-dimer levels and increased mortality was observed across evaluated subgroups. Higher D-dimer was associated with increased mortality (pooled HR: 1.90 [95% CI 1.63–2.20]), shorter PFS (pooled HR: 1.46 [1.22–1.76]), and DFS (2.02 [1.56–2.62]).[51] In summary, these studies imply an independent prognostic utility of D-dimer across different cancer types and independently of key clinical covariables.

Perisanidis et al. evaluated the prognostic role of pretherapeutic fibrinogen levels in patients with cancer in a large-scale meta-analysis including a total of 52 observational studies and 15371 patients. In a pooled analysis, including only studies that provide risk estimates adjusted for confounders in multivariable analysis, mortality was increased with higher baseline fibrinogen levels (pooled HR: 1.69 [95% CI 1.48–1.92]), with the largest observed effect in renal cell carcinoma (HR: 2.22), head and neck cancer (HR: 2.02), and colorectal cancer (HR: 1.89). These results prevailed in subgroup analyses, separately assessing metastatic and nonmetastatic cancer. Further, higher baseline fibrinogen levels were associated with decreased DFS (pooled multivariable-adjusted HR: 1.53 [1.32–1.74]). However, between-study heterogeneity was high and different biomarker cutoffs were used in included studies, limiting these pooled analyses.[52]

Other biomarkers evaluated in heterogeneous cohorts of patients with cancer include, among others, sP-selectin. In a prospective cohort study (n = 705), a 30% increased risk of mortality was observed for patients with sP-selectin levels in the highest quartile compared to the remainder of patients.[53] Further, for levels of protein C, an independent association between lower levels and increased mortality was observed in a post-hoc analysis of a clinical trial (n = 477).[54] Last, high levels of TAT, fibrin monomers, and F1+2 predicted an increased risk of mortality in a prospective cohort study.[55]

In a subanalysis of a prospective cohort study including patients with newly diagnosed or recurrent cancer, longitudinal biomarker measurements over the course of systemic chemotherapy were performed in 112 patients. Patients who had complete remission of disease during the observation period had significantly lower levels of D-dimer, F1+2, and fibrinogen over time compared with those without complete remission, whereas no such association was observed for levels of FVIII, sP-selectin, and peak TG.[56] These observations indicate the potential for monitoring treatment response via longitudinal measurement of hemostatic biomarkers over the course of systemic therapy.

2.2 | Lung cancer

The blood coagulation system is highly involved in the development and progression of lung cancer.[35,57] Accordingly, numerous studies consistently reported an association between hemostatic biomarkers and more advanced stage of disease, a higher number of metastatic organ sites, and worse performance status.[58–61] Further, several hemostatic biomarkers were identified that efficiently and independently predict survival and therapy response in different treatment settings in lung cancer patients.

In a meta-analysis, aggregating data from 11 studies including 1625 patients, OS was lower with elevated D-dimer levels (pooled HR: 2.06 [95% CI 1.64–2.58]). However, between-study heterogeneity was high and cutoffs for defining elevation of D-dimer differed.[62]

In a prospective cohort study, the prognostic and predictive utility of a panel of hemostatic and inflammatory biomarkers was evaluated in patient with advanced lung cancer (83% non-small cell lung cancer [NSCLC]) before systemic chemotherapy (n = 277). An independent association with OS was observed for baseline levels of D-dimer (adj. HR per double: 1.50 [95% CI 1.29–1.75]), sP-selectin (adj. HR: 1.42 [1.09–1.83]), and FVIII: (adj. HR: 1.46 [1.08–1.98]), whereas no significant association was observed for F1+2, FGEN, or peak TGA. D-dimer levels were further associated with PFS (adj. HR per double: 1.34 [1.16–1.53]), as were levels of F1+2 (1.22 [1.04–1.44]).[63]

Further, a retrospective cohort study including 232 patients with operable NSCLC, pre-surgical levels of D-dimer were independently associated with 1-year mortality (adj. HR: 1.54 [95% CI 1.11–2.78]).[64]

In a retrospective cohort study of patients with small-cell lung cancer (n = 393), elevated baseline levels of D-dimer were independently associated with decreased OS (adjusted HR: 1.58 [95% CI 1.14–2.12]) and PFS (adj. HR: 1.42 [1.09–1.86]). Further, normalization of elevated baseline D-dimer levels after two chemotherapy cycles was associated with favorable OS and PFS compared with patients with ongoing high levels during chemotherapy.[60] The feasibility of using longitudinal D-dimer levels for oncologic prediction was further confirmed for novel targeted treatment approaches in a cohort study including 52 patients undergoing EGFR-targeted therapy. A decrease in D-dimer during therapy was associated with longer PFS (adj. HR: 0.39 [95% CI 0.16–0.91]), OS (adj. HR: 0.33

[95% CI 0.13–0.82]) and significantly higher DCR at restaging during therapy.[65]

The prognostic utility of fibrinogen levels in lung cancer patients was evaluated in a meta-analysis, combining results of 16 studies including 6881 patients. Higher fibrinogen levels were associated with OS (pooled HR: 1.38 [95% CI 1.22–1.55]) and PFS/DFS (pooled HR: 1.29 [1.01–1.65]), which was confirmed in a sensitivity analysis for a fibrinogen cutoff at 400 mg/dl.[66]

In a cohort study using tissue samples of 53 patients with NSCLC after curative resection, tumoral expression of TF was associated with decreased OS in multivariable analysis (adjusted HR: 2.2 [95% CI 1.1–4.2]), with a median survival of 5.5 years with below-median TF expression compared with 2.2 years in patients above the median. Further, expression of TF was associated with higher disease stage and distinct oncogenic alterations.[14]

2.3 | Colorectal cancer

Hemostatic biomarkers, most prominently D-dimer and fibrinogen, were frequently investigated in patients with colorectal cancer (CRC) and an association between biomarker levels with disease stage and characteristics of the primary tumor were found.[67–70] Further, consistent data exist on the role of different hemostatic biomarkers for the prediction of mortality, recurrence risk, and therapy response.

In a meta-analysis including 37 studies and 12 359 patients, the prognostic role of D-dimer and fibrinogen in patients with gastrointestinal cancers was evaluated. An association with mortality was found for elevated levels of D-dimer (pooled HR: 2.06 [95% CI 1.79–2.38]) and fibrinogen (pooled HR: 1.60 [1.44–1.79]). However, studies differed in underlying type and stage of cancer and cutoffs for definition of elevated biomarkers. In a subanalysis, including only studies in CRC, the prognostic role of D-dimer (pooled HR: 2.32 [1.89–2.85]), and fibrinogen (pooled HR: 2.20 [1.24–3.90]) was confirmed.[71]

In a prospective cohort study ($n = 93$) in resectable CRC patients, preoperative levels of D-dimer were associated with advanced disease stage, tumor invasion depth, and postoperative survival.[68] Accordingly, in another prospective cohort study on CRC patients undergoing curative surgery ($n = 153$), higher preoperative levels of D-dimer (cutoff: 0.3 mg/dl) were independently prognostic for decreased 1-year survival (adj. HR: 3.6 [95% CI 1.3–9.9]).[72] Further, in CRC patients undergoing surgery, preoperative levels of fibrinogen were identified as independent predictors for OS and cancer-specific mortality, and preoperative sP-selectin levels predicted for cancer-recurrence and cancer-specific mortality.[70,71]

In patients with metastatic CRC undergoing systemic antineoplastic therapy, different studies identified D-dimer as prognostic marker. In a post-hoc analysis of a phase II clinical trial in previously untreated patients with metastatic colorectal cancer ($n = 98$), baseline D-dimer was independently associated with OS, but not PFS. However, postbaseline elevated levels of D-dimer during chemotherapy were associated with disease progression more reliably than levels of CEA, a routine tumor marker used to monitor recurrence risk and treatment response in CRC.[73] In a prospective cohort study, including 99 patients with metastatic CRC before systemic chemotherapy, a panel of hemostatic biomarkers was evaluated for its prognostic and predictive utility. An independent association with OS was identified for pretherapeutic levels of D-dimer (adj. HR per double: 1.40 [95%CI: 1.18–1.65]), FVIII (HR: 2.06 [1.28–3.30]), sP-selectin (HR: 1.55 [1.07–2.24]), and F1 + 2: (HR: 1.64 [1.10–2.46]), a nonsignificant association with fibrinogen (HR: 1.94 [0.98–3.83]), and no association with peak TG. Further, elevated hemostatic biomarkers were associated with a numerical but non-significant decrease in PFS, and higher baseline levels of FVIII and F1 + 2 were associated with a decreased DCR during chemotherapy.[74]

The expression of TF was reported as predictor of metastatic potential, tumor recurrence after curative resection, and as prognostic marker in patient with CRC.[75,76] However, in a subanalysis of a prospective cohort study including 126 patients with CRC, peripheral EV-TF levels were not associated with mortality (adj. HR: 1.2 [95% CI 0.9–1.6]).[23]

2.4 | Pancreatic cancer

Pancreatic cancer is characterized by the highest thrombotic risk among all tumor types. Different pathophysiological pathways were identified that contribute to systemic hypercoagulability and in return support tumor-promoting mechanisms in pancreatic cancer.[77] These observations provide a robust biological rational to use hemostatic biomarkers for the prediction of oncologic outcome in patient with pancreatic cancer.

In a retrospective cohort study including patients with pancreatic cancer undergoing R0 resection ($n = 282$), elevated preoperative levels of D-dimer and fibrinogen predicted for shorter OS (adjusted HRs: 1.36 [95% CI 1.02–1.80], and 1.60 [95%CI: 1.20–2.14], respectively).[78] In a prospective cohort study including 67 patients with pancreatic ductal adenocarcinoma (33% stage IV), higher pretherapeutic fibrinogen levels were observed in metastatic cancer, and elevated fibrinogen levels were independently associated with decreased OS (adj. HR: 1.81 [95% CI 1.12–3.23]).[79]

EV-TF was identified as independent prognostic biomarker in several studies. In a retrospective cohort study, patients with pancreato-biliary cancer were included ($n = 117$; 68% pancreatic, 29% biliary; 45% stage IV). Elevated baseline levels of EV-TF (≥2.5 pg/mL) were independently associated with decreased survival (adj. HR: 2.5 [95% CI 1.4–4.5]), with a median OS of 3.2 months with high levels compared with 7.6 months with lower levels.[80] In a prospective cohort study, the prognostic utility of EV-TF was evaluated in highly thrombogenic tumors types with newly diagnosed or recurrent cancer. In patients with pancreatic cancer ($n = 60$), an independent association between baseline EV-TF and mortality was observed (adj. HR: 1.7 [95% CI 1.3–2.1]), with a 1-year survival probability of 59% in patients with low EV-TF levels (<75th percentile) compared with only 15% in those with high baseline EV-TF levels (≥75th percentile).[23]

In a recent analysis of the same prospective observational cohort study, a comprehensive panel of hemostatic biomarkers was evaluated for its association with OS and response to palliative chemotherapy in with pancreatic cancer ($n = 145$).[81] Higher baseline levels of D-dimer, EV-TF, sP-selectin, and PAI-1 were identified as independent predictors of increased mortality, whereas no association was observed for levels of F1 + 2, fibrinogen, and parameters of the TGA. Further, elevated D-dimer emerged as efficient and independent predictor of shorter PFS (adj. HR: 1.29 [95% CI 1.03–1.61]) and decreased DCR during treatment (adj. OR: 0.61 [0.38–0.99]) in the subgroup of patients initiating palliative chemotherapy after study inclusion ($n = 95$).[81]

2.5 | Breast cancer

Patients with breast cancer have a lower risk of cancer-associated VTE compared with other tumor types.[4] Nevertheless, systemic hemostatic activation is observed in patients with breast cancer despite the clinical absence of overt thrombotic manifestation. Further, the hemostatic system is mechanistically involved in breast cancer development and progression.[82]

Accordingly, clinical and pathological characteristics of breast cancer seem to correlate well with systemic levels of hemostatic biomarkers. In a cohort study including 102 patients with invasive breast cancer, preoperative D-dimer levels were associated with lymph node involvement, the presence of lymphovascular invasion, and disease stage.[83] In a cohort study including 235 patients with early-stage breast cancer (stages I-IIa), the prognostic role of pretherapeutic levels of PAI-1, F1 + 2, TAT, FVIII and D-dimer were investigated. Elevated levels of D-dimer and FVIII were associated with significantly decreased OS in univariable analysis. This association prevailed upon multivariable adjustment for D-dimer (adj. HR: 3.17 [95% CI: 1.13–8.94]), whereas a nonsignificant increase in risk was observed for FVIII (adj. HR: 2.15 [0.90–5.15]).[84] In another cohort study including patients with breast cancer who were either operable ($n = 23$) or had untreated or progressive metastatic disease ($n = 84$), D-dimer levels correlated with tumor load, number of metastatic sites and cancer progression dynamics, with higher levels in patients with rapid tumor progression defined as doubling in size of target lesions in less than 3 months. Further, D-dimer was identified as independent prognostic marker.[85]

In a retrospective cohort study including 102 patients with HER-2 positive breast cancer undergoing trastuzumab treatment, elevated baseline fibrinogen (>2.88 g/L) was associated with histological grade and lower levels of PTEN expression, a tumor suppressor known to be involved in breast cancer carcinogenesis. Elevated fibrinogen levels predicted for shorter OS (adj. HR: 7.55 [95% CI 1.18–48.20]) and DFS (adj. HR: 6.41 [1.78–11.97]).[86]

More recently, the multicenter, prospective observational HYPERCAN study provided important results on the clinical application of coagulation tests to stratify disease outcomes in patients with breast cancer.[87] In a cohort of 522 patients with surgically resected high-risk breast cancer patients, TG-potential measured before the initiation of systemic chemotherapy was identified as independent predictor for early disease recurrence and incorporated in a risk prediction model together with key clinical covariables.[88] Further, in a cohort of 701 patients with early-stage breast cancer, prechemotherapy levels of D-dimer, fibrinogen, F1 + 2 and FVIIa/AT levels were evaluated, with baseline systemic levels of F1 + 2 identified as independent predictor of disease recurrence.[89]

In a cohort study including 152 treatment naive breast cancer patients, lower tumoral TFPI expression was associated with dismal clinical outcomes, and plasma TFPI levels were associated with primary tumor characteristics.[90] Further, in another study including 156 patients with breast cancer who underwent primary resection, low or absent expression of TFPI-2 predicted for higher risk of tumor recurrence and poor survival.[91]

2.6 | Other cancer types

Hemostatic biomarkers were evaluated in various additional tumor types. In patients with ovarian cancer, the results of a meta-analysis including data from 15 studies and 1437 patients suggest elevated baseline D-dimer as prognostic biomarker for increased mortality (pooled HR: 1.32 [0.90–1.95], restricted to studies with $n > 100$: HR 1.80 [1.28–2.52]).[92] A cohort study including 190 patients with epithelial ovarian cancer found an independent association with mortality of elevated pre-treatment levels of D-dimer (adj. HR: 1.64 [1.03–2.63]), platelet count (adj. HR: 1.64 [1.00–2.68]) and fibrinogen (adj. HR: 2.12 [1.32–3.41]), with conflicting data regarding PFS (adj. HR: D-dimer: 1.23 [0.80–1.90], platelet count: 1.68 [1.08–2.62], fibrinogen: 1.71 [1.12–2.61]).[93] In a small longitudinal analysis, the evolution of D-dimer and CA-125 levels were evaluated in 26 patients with ovarian cancer during systemic therapy, identifying the decrease in both markers as predictor for disease remission.[94]

In a retrospective cohort study including patients with gastric cancer undergoing gastrectomy ($n = 1196$), presurgical levels of fibrinogen were associated with stage and lymph node involvement of the cancer and was independently associated with decreased OS (adj. HR: 1.36 [1.14–1.62]).[95] Another study including 247 patients undergoing gastrectomy (curative: $n = 168$, palliative: $n = 46$) found an association between presurgical D-dimer levels and key cancer characteristics including tumor size, invasion depth, lymph node metastasis, peritoneal involvement, and distant metastasis. Further, elevated D-dimer was identified as independent prognostic biomarker for increased mortality (adj. HR: 2.28 [1.36–3.81]).[96] Accordingly, in a post-hoc analysis of a randomized controlled trial ($n = 666$), evaluating D-dimer measurements at different pre- and postsurgical timepoints, an association between elevated D-dimer levels and decreased OS and DFS was reported, consistently across different measurement timepoints.[97] In a retrospective cohort study including patients with metastatic gastric cancer initiating palliative chemotherapy ($n = 46$), pretreatment D-dimer levels were associated with OS. Further, patients with radiological disease control at restaging

had significantly lower D-dimer levels compared with the baseline measurment.[98]

In patients with endometrial cancer a cohort study including 942 patients undergoing surgery reported an independent association between pretreatment fibrinogen levels and OS, whereas levels of D-dimer, APTT, and PT were not prognostic.[99] Accordingly, in a multicenter retrospective cohort study ($n = 436$) pretreatment fibrinogen levels were identified as independent predictor of OS and DFS.[100] In patients with cervical cancer, pretreatment D-dimer levels were reported as independent predictor of OS (adj. HR: 2.33 [95% CI 1.12–5.50]).[101] Further, a large cohort study including patients with renal cell carcinoma identified D-dimer and fibrinogen levels as independent prognostic and predictive biomarkers for OS and DFS.[102]

3 | DISCUSSION

In summary, hemostatic biomarkers seem to have a prognostic and predictive role for survival and therapy response in patients with cancer. In combination with the underlying biological rationale, linking the hemostatic system to mechanisms of cancer development and progression, hemostatic biomarkers represent promising candidates to support risk-stratified oncologic decision making in the future. However, to date, several important limitations exist that prevent their current application in clinical practice.

First, the overall scientific quality of studies investigating hemostatic biomarkers in cancer patients, based on study design and methodology, is highly heterogeneous, with many studies limited in generalizability because of small sample sizes, exploratory nature, methodological flaws, or retrospective design. This observation might be explained by the routine availability of some of the investigated markers, making them attractive to explore their predictive utility in retrospect from existing data. However, well-designed studies exist that overcome these limitations. Further, because of the high heterogeneity in study design, applied cutoff values for the definition of elevated biomarker levels, and used methodology including selection of variables for multivariable adjustment, a comparative interpretation of the results from different studies is challenging and the quality of meta-analyses pooling the results from individual studies is highly limited a priori. In several meta-analyses, evaluating D-dimer and fibrinogen in different cancers, these limitations were partially overcome by the conduct of rigorous sensitivity and subgroup analyses, limiting data aggregation to specific subgroups according to cancer types, stage, or used cutoff values.

Second, hemostatic biomarkers have important limitations for clinical implementation as of their low specificity. For example, hemostatic biomarkers might be largely affected by anticoagulation therapy, a recent history of thrombotic events, a systemic pro-inflammatory state, pregnancy, and other factors. In addition, especially regarding systemic levels of fibrinogen, decreased levels might occur in the setting of cancer-associated disseminated intravascular coagulation (e.g., in acute promyelocytic leukemia or prostate cancer), which needs to be considered when evaluating fibrinogen levels for clinical prediction purposes. Consequently, clinical application of hemostatic biomarkers necessitates a rigorous definition of criteria on when and when not to use these biomarkers for prediction purposes. However, especially in the setting of malignancy, this low specificity based on the interconnectedness of hemostasis with various physiological systems and processes might actually contribute to the general prognostic and predictive value of these biomarkers because systemic levels might canonically reflect complex systemic dysregulations. Thereby, hemostatic biomarkers might therefore be regarded as "comprehensive" oncologic biomarkers, broadly indicating more aggressive cancers, worse prognosis, sicker patients, and dismal outcomes, in opposition to highly specific oncologic biomarkers used to tailor personalized treatment approaches such as genetic alterations, the expression of targetable proteins on tumor cells, or systemic levels of circulating tumoral DNA. Both types of biomarkers have inherent advantages and disadvantages and could therefore be used complementarily to advance risk-stratified patient care in the future.

Third, the clinical application of several investigated hemostatic biomarkers is currently limited by methodological requirements. For example, biomarkers including parameters from the TGA or EV-TF activity are not available in most centers and their measurement is currently limited because of methodological aspects including between-assay variability and labor-extensive measurements. In contrast, other hemostatic biomarkers represent routinely used parameters, most prominently D-dimer and fibrinogen, and have a low logistical and financial burden of clinical application.

Last, the observed prognostic utility of these biomarkers has been mostly evaluated in the setting of solid cancers, which highly limits the extrapolation of these observations to hematologic malignancies.

Synoptically, hemostatic biomarkers have the potential to improve personalized patient care in patients with cancer. However, based on currently available data, the potential for clinical implementation seems to vary based on individual hemostatic biomarkers and the oncologic treatment setting. For example, consistent data suggest D-dimer and fibrinogen levels as independent prognostic biomarkers in a tumor-type agnostic fashion, with the most robust data available in lung cancer and gastrointestinal cancers. In contrast, other biomarkers might represent more tumor-type specific markers. For example, levels of EV-TF have been repeatedly shown to have a prognostic utility specifically in patients with pancreatic cancer.[80,81] Further, levels of PAI-1 have recently been identified as cancer-type specific prothrombotic biomarker in patients with pancreatic cancer, which further seems to represent a strong and independent predictor of OS and therapy response in this setting.[26,81]

Regarding the most promising therapeutic setting for potential clinical application of hemostatic biomarkers, several considerations apply. Speculatively, based on available data, the most promising clinical settings might be the pretherapeutic prognostication of OS to contribute to the identification of distinct prognostic subgroups of patients, and the evaluation of longitudinal trends of hemostatic

biomarker levels over the course of antineoplastic therapies, where increasing levels of biomarkers might indicate underlying cancer progression dynamics. Thereby, integrating hemostatic biomarkers in clinical decision making might ultimately improve patient care by (1) the potential to more accurately identify poor prognostic subgroups of patients that might benefit from more intensive medical care, (2) an increased ability to tailor personalized therapeutic approaches by estimating pre-therapeutic response probabilities, and (3) by raising the suspicion for disease progression or recurrence based on longitudinal trends in hemostatic biomarkers. However, before implementing hemostatic biomarkers in routine clinical care, these approaches need to be tested for their validity and especially their clinical utility, ideally in the setting of prospective clinical studies and interventional studies.[103]

3.1 | Future directions

Consistent data exist on the overall prognostic value of hemostatic biomarkers, especially for D-dimer and fibrinogen, in various oncologic settings. However, before potential future clinical utilization, the prognostic and predictive role of a candidate hemostatic biomarkers needs to be characterized in refined oncological treatment settings, including different tumor types, stages, and treatment indications. To date, in contrast to a robust association between different hemostatic biomarkers with OS, the association with response to anticancer therapy is less clear and seems to be specific for the evaluated treatment scenario, tumor type, and investigated hemostatic biomarker. To further advance research on hemostatic biomarkers for the prediction of oncologic outcomes, dedicated studies need to be conducted in refined oncologic treatment scenarios, controlling for potential confounding factors. Further, the derivation and validation of biomarker-based prediction models, potentially also incorporating key clinical covariables, might increase the predictive power. Additionally, interventional studies and clinical trials in oncology should implement the measurement of hemostatic biomarkers in the future to allow analyzing their predictive utility in a controlled setting and thereby help identify relevant clinical subgroups based on hemostatic biomarkers levels. Further, the ideal timepoint of biomarker measurements needs to be defined to make the clinical application of hemostatic biomarkers reproduceable. These timepoints might comprise of baseline, pretherapeutic measurement only, or might consist of multiple longitudinal measurements that might help identify treatment failure and disease progression or recurrence based on elevation of hemostatic biomarkers over time.

4 | CONCLUSION

In conclusion, different hemostatic biomarkers represent promising candidates for potential future clinical implementation in risk-stratified oncological decision making. Currently, data from cohort studies exist that suggest a prognostic and predictive utility of hemostatic biomarkers, mostly D-dimer and fibrinogen, in various tumor types and therapeutic settings. However, interventional studies that investigate hemostatic biomarkers in risk-stratified therapeutic decision making are currently lacking, limiting their current use in clinical practice. Consequently, the next steps to identify and confirm the clinical utility of hemostatic biomarkers in refined oncologic treatment scenarios should be taken. Thereby, hemostatic biomarkers might ultimately be used as prognostic and predictive biomarkers for survival and therapy response in patient with cancer, which could contribute to personalized, risk-stratified patient management in the future.

AUTHOR CONTRIBUTIONS

F.M. contributed to manuscript conceptualization, literature research, and manuscript writing; CA: contributed to manuscript conceptualization and manuscript writing.

CONFLICT OF INTEREST

Florian Moik: No potential conflict of interest. Cihan Ay: Honoraria and personal fees for lectures and participation in advisor boards from Bayer, BMS, Daiichi-Sankyo, Pfizer, and Sanofi.

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