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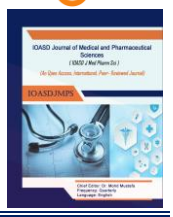

Venous Thromboembolism Risk and Coagulation Markers in Rare Breast Tumors: A Perspective

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ABSTRACT

Venous thromboembolism (VTE) is a frequent and serious complication in cancer patients, with risk varying according to tumor subtype and biology. Rare breast tumors, including metaplastic, secretory, adenoid cystic, and phyllodes tumors, remain understudied regarding their association with coagulation abnormalities and thrombotic risk. This perspective synthesizes current knowledge on the pathophysiology of coagulation activation, the prognostic value of coagulation markers such as D-dimer and thrombin generation, and the clinical implications for VTE risk management in patients with rare breast tumors. Recognizing the distinct coagulation profiles and thrombotic tendencies in these tumors is critical to refining risk stratification and guiding personalized thromboprophylaxis. Future research focusing on molecular mechanisms and biomarker validation is essential to improve clinical outcomes and reduce thrombotic morbidity in this unique patient population.

Keywords: Venous thromboembolism, Coagulation markers, Rare breast tumors, Hypercoagulability, Thrombosis risk.

Review Article

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ABBREVIATIONS

D-dimer – Fibrin degradation product
F1+2 – Prothrombin fragment 1+2
IUGR – Intrauterine growth restriction
MPV – Mean platelet volume
PAI-1 – Plasminogen activator inhibitor-1
PlGF – Placental growth factor
Protein C – Natural anticoagulant protein C
Protein S – Natural anticoagulant protein S
sFlt-1 – Soluble fms-like tyrosine kinase-1
TFPI – Tissue factor pathway inhibitor
TAT – Thrombin-antithrombin complex

INTRODUCTION

Venous thromboembolism (VTE), encompassing deep vein thrombosis and pulmonary embolism, represents a major cause of morbidity and mortality in cancer patients worldwide [1-2]. The risk of VTE is markedly elevated in malignancy due to tumor-mediated activation of the coagulation cascade, inflammation, and vascular injury. While breast cancer as a whole is associated with a moderate risk of thrombosis, emerging evidence suggests that rare breast tumor subtypes may have distinct coagulation profiles and VTE risk patterns that remain poorly characterized [3-5]. Rare breast tumors such as metaplastic, secretory, adenoid cystic, and phyllodes tumors constitute a heterogeneous group with unique histopathological and molecular features. These tumors often exhibit aggressive behavior or atypical clinical presentations compared to more common invasive ductal carcinomas. Their rarity and biological diversity pose challenges for diagnosis, treatment, and risk assessment, including the evaluation of thrombotic risk, which is critical given the potential impact of VTE on patient outcomes [6-7].

Cancer-associated hypercoagulability is driven by multiple mechanisms, including tumor expression of procoagulant factors like tissue factor (TF), secretion of prothrombotic microparticles, and systemic inflammatory responses. In rare breast tumors, specific molecular alterations and stromal interactions may further modulate these pathways, contributing to unique coagulation imbalances that predispose to thrombosis. However, data regarding coagulation activation and its clinical relevance in these tumors remain limited and

fragmented [8-9]. Coagulation markers such as D-dimer, thrombin-antithrombin complexes, and platelet counts serve as useful indicators of coagulation activation and fibrinolysis in cancer patients. Elevated levels of these markers have been linked to increased VTE risk and poor prognosis in various malignancies. Nevertheless, their role in rare breast tumors has not been extensively explored, limiting their application in risk stratification and clinical decision-making for this subgroup [10-11].

Clinically, the management of VTE risk in patients with rare breast tumors is challenging due to the lack of subtype-specific guidelines and the variable use of chemotherapy, surgery, and radiotherapy. These treatments, combined with patient-related factors such as immobility and comorbidities, further complicate thromboprophylaxis strategies. Personalized approaches integrating coagulation biomarkers with clinical risk factors may improve VTE prevention and patient outcomes [12-14]. This perspective aims to synthesize current knowledge on VTE risk and coagulation markers in rare breast tumors, exploring underlying pathogenic mechanisms, the predictive value of biomarkers, and clinical management considerations. By highlighting gaps in the literature, we hope to stimulate further research.

Pathogenic Mechanisms of Coagulation Activation in Rare Breast Tumors

Cancer-associated hypercoagulability arises from a complex interplay of tumor-specific factors, host responses, and treatment-related influences that collectively disrupt normal hemostatic balance. In rare breast tumors, this coagulation imbalance appears to be driven by distinctive molecular and cellular mechanisms reflective of their unique biology [15-16]. One of the principal contributors to coagulation activation is the aberrant expression of TF by tumor cells. TF is a transmembrane glycoprotein that serves as the primary initiator of the extrinsic coagulation cascade by binding circulating factor VII/VIIa, leading to downstream thrombin generation and fibrin clot formation. Several rare breast tumor subtypes, particularly metaplastic carcinoma, demonstrate elevated TF expression, which correlates with aggressive clinical behavior and enhanced thrombotic potential [17].

Beyond TF expression, rare breast tumors release procoagulant extracellular vesicles or microparticles enriched with TF and other coagulation factors. These microparticles circulate systemically, propagating coagulation activation distal to the primary tumor site and contributing to a hypercoagulable state. Their presence also facilitates cross-talk between tumor cells, endothelial cells, platelets, and immune cells, fostering a microenvironment conducive to thrombosis and tumor progression [18-19]. Inflammatory cytokines produced by tumor and stromal cells further amplify coagulation activation. Cytokines such as interleukin-1β, tumor necrosis factor-α, and vascular endothelial growth factor (VEGF) upregulate TF expression on both tumor and endothelial cells, while also enhancing platelet activation and aggregation. This inflammatory milieu intensifies thrombin generation and promotes fibrin deposition within the tumor microenvironment [20-22].

Moreover, the unique stromal composition of certain rare breast tumors, such as phyllodes tumors with their abundant fibroblastic stroma, may influence coagulation dynamics through secretion of matrix metalloproteinases and growth factors that modulate endothelial integrity and coagulation factor expression. This stromal-tumor interaction potentially exacerbates local hypercoagulability and vascular permeability, increasing thrombosis risk [23-24]. Treatment modalities, including surgery, chemotherapy, and radiotherapy, commonly employed in managing rare breast tumors, also contribute to coagulation activation. Tissue injury from surgery exposes subendothelial procoagulant surfaces, while chemotherapy and radiotherapy induce endothelial dysfunction and inflammatory responses that potentiate thrombin generation and platelet activation (Table 1) [25-26].

Table 1: Pathogenic Mechanisms of Coagulation Activation in Rare Breast Tumors

Pathogenic Mechanism	Key Mediators / Biomarkers	Effect on Coagulation	Clinical Implications
Tissue Factor (TF) Overexpression	TF, Factor VII	Initiates extrinsic coagulation cascade	Increased thrombin generation, risk of venous thromboembolism (VTE)
Cancer-Associated Inflammation	IL-6, TNF-α, CRP	Endothelial activation, platelet adhesion	Hypercoagulable state, thrombosis, tumor progression
Tumor Cell Microparticles	TF-positive microparticles	Propagate thrombin generation	Microvascular thrombosis, systemic coagulation activation
Platelet-Tumor Cell Interaction	P-selectin, integrins	Platelet aggregation and activation	Enhanced tumor metastasis, thrombotic complications
Impaired Natural Anticoagulants	Protein C/S ↓, Antithrombin III ↓	Reduced inhibition of thrombin	Increased risk of VTE, disseminated intravascular coagulation (DIC)
Fibrinolytic Imbalance	PAI-1 ↑, tPA ↓	Impaired clot breakdown	Persistent microthrombi, vascular occlusion, tumor hypoxia
Angiogenesis-Related Coagulation	VEGF, PlGF	Endothelial remodeling and procoagulant surface	Supports tumor growth, promotes local thrombosis

Coagulation Markers as Predictors of VTE Risk

Accurate prediction of VTE risk in cancer patients is crucial for timely prophylaxis and improved clinical outcomes. In the context of rare breast tumors, coagulation biomarkers serve as valuable tools for assessing the hypercoagulable state and stratifying patients according to their thrombotic risk [27-29]. Among the most extensively studied coagulation markers is D-dimer, a fibrin degradation product reflecting active clot formation and breakdown. Elevated D-dimer levels have been consistently associated with increased VTE risk across diverse malignancies, and preliminary data suggest that patients with rare breast tumors exhibiting elevated D-dimer may similarly be at heightened thrombotic risk. D-dimer measurement is widely available, cost-effective, and offers real-time insight into ongoing coagulation and fibrinolysis [30-31].

Thrombin generation assays provide a dynamic evaluation of coagulation potential by measuring the capacity of plasma to generate thrombin, the key enzyme responsible for fibrin formation. Increased thrombin generation correlates with cancer aggressiveness and thrombotic propensity. In rare breast tumors, enhanced thrombin generation may reflect tumor-induced activation of coagulation pathways, although specific studies remain limited. Incorporating thrombin generation profiles could enhance risk stratification beyond static markers [32-33]. Other markers such as prothrombin fragment 1+2 (F1+2), which indicates thrombin formation, and thrombin-antithrombin (TAT) complexes, representing thrombin neutralization, have also shown promise in identifying cancer patients at risk of VTE. Elevated platelet counts and markers of platelet activation are additional indicators of prothrombotic states, given the pivotal role of platelets in tumor cell survival and metastasis [34-35]. Therefore, integrating multiple biomarkers alongside clinical risk factors—such as tumor stage, performance status, and treatment modalities—may improve predictive accuracy. Prospective studies are needed to validate coagulation marker thresholds specific to rare breast tumor subtypes and establish standardized protocols for their clinical use. [36-37]

Clinical Implications and Management Strategies

VTE poses a substantial clinical challenge in patients with rare breast tumors, necessitating vigilant risk assessment and tailored management strategies. Given the elevated morbidity and mortality associated with cancer-associated thrombosis, understanding the unique coagulation dynamics in these uncommon tumor subtypes is imperative for optimizing patient outcomes [38]. Current clinical guidelines for VTE prophylaxis in cancer patients are predominantly derived from studies on more common malignancies, often without specific recommendations for rare breast tumors. This gap leaves clinicians reliant on extrapolating data, which may inadequately address the distinct thrombotic risks posed by tumors such as metaplastic, secretory, adenoid cystic, and phyllodes carcinomas. Consequently, there is an unmet need for personalized risk stratification models that incorporate tumor biology, coagulation marker profiles, and treatment-related factors [39].

Routine assessment of coagulation markers—including D-dimer and thrombin generation—can enhance the identification of patients at heightened risk for VTE, thereby guiding decisions regarding thromboprophylaxis initiation and intensity. For high-risk patients, low molecular weight heparins (LMWH) remain the cornerstone of prophylaxis due to their proven efficacy and safety in cancer-associated thrombosis. Emerging direct oral anticoagulants (DOACs) offer additional options but require cautious use given potential drug interactions and bleeding risks, especially in patients undergoing surgery or chemotherapy [40]. Management strategies must also consider the timing and context of interventions. Perioperative thromboprophylaxis is critical in rare breast tumor surgeries, where tissue manipulation and immobilization amplify thrombotic risk. Likewise, systemic therapies—including chemotherapy and targeted agents—may exacerbate coagulation abnormalities, necessitating close monitoring and prophylactic adjustments [41].

Multidisciplinary collaboration involving oncologists, hematologists, surgeons, and primary care providers is essential to balance thrombosis prevention with bleeding risk, optimize anticoagulant selection, and ensure patient adherence. Patient education on VTE signs and symptoms further contributes to early detection and prompt management [42]. Integrating ongoing research findings into clinical practice through institutional protocols and consensus guidelines will improve care consistency. Prospective studies evaluating thromboprophylaxis efficacy specifically in rare breast tumor populations are urgently needed to refine management algorithms and improve patient safety [43].

Future Directions

The complex relationship between VTE risk and coagulation abnormalities in rare breast tumors remains incompletely understood, underscoring the need for focused research efforts. Future studies should aim to delineate the molecular and cellular mechanisms underlying coagulation activation specific to rare breast tumor subtypes, leveraging advanced techniques such as genomics, proteomics, and single-cell analyses to uncover novel prothrombotic pathways [44]. Large-scale prospective cohort studies are essential to establish the incidence and timing of VTE events in patients with rare breast tumors, as current data are largely retrospective and limited by small sample sizes. Such studies should incorporate comprehensive coagulation marker profiling alongside clinical variables to develop validated, subtype-specific risk prediction models. These models will be invaluable for guiding personalized

thromboprophylaxis strategies, optimizing the balance between efficacy and safety [45].

Additionally, randomized controlled trials evaluating the effectiveness and safety of anticoagulant therapies—including low molecular weight heparins and direct oral anticoagulants—in patients with rare breast tumors are needed. These trials should consider the unique tumor biology, treatment regimens, and bleeding risks inherent to this population to inform evidence-based guidelines [46]. Investigations into the impact of emerging cancer therapies, such as immunotherapy and targeted agents, on coagulation pathways and VTE risk in rare breast tumors represent another important research avenue. Understanding how these treatments influence hypercoagulability will facilitate integrated management approaches and minimize thrombotic complications [47].

Moreover, collaborative registries and multicenter consortia focused on rare breast tumors can accelerate data collection and knowledge dissemination, overcoming challenges posed by tumor rarity and heterogeneity. Integration of real-world evidence with clinical trial data will enhance the generalizability and applicability of findings [48]. Patient-centered research exploring education, awareness, and adherence to thromboprophylaxis regimens will complement biomedical advances, ensuring that improved diagnostic and therapeutic strategies translate into better patient outcomes [49].

CONCLUSION

VTE represents a significant and often underappreciated complication in patients with rare breast tumors, driven by complex coagulation imbalances intrinsic to tumor biology and influenced by treatment-related factors. Although evidence remains limited, emerging data suggest that distinct coagulation marker profiles—such as elevated D-dimer and enhanced thrombin generation—may serve as valuable predictors of thrombotic risk in this heterogeneous group. Personalized risk assessment incorporating these biomarkers alongside clinical parameters is crucial for optimizing thromboprophylaxis and improving patient outcomes. Bridging the current knowledge gaps requires dedicated research focused on understanding the pathogenic mechanisms of coagulation activation specific to rare breast tumor subtypes and validating predictive biomarkers in prospective cohorts. Multidisciplinary collaboration and well-designed clinical trials are essential to establish evidence-based guidelines tailored to this unique population.

Conflicts of Interest

The author declares no conflict of interest

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