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Coagulation Markers as Predictive and Prognostic Factors in Carcinoma Breast Patients with Lymph Node Metastasis

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Article History	Abstract
	Objective: *The purpose of this prospective observational study was to evaluate the predictive and prognostic value of coagulation markers in patients with lymph node metastases and cancer of the breast, as well as their associations with important histopathologic criteria.* ***Methods***: *Between December 2020 and July 2022, 100 patients from the surgery department of a tertiary hospital were enrolled in the study. D-dimer, fibrinogen, and prothrombin time were assessed as coagulation indicators. Documented histopathologic characteristics included tumor grade, size, lymph node involvement, and estrogen receptor status. Chi-square tests, t-tests, Kaplan-Meier survival curves, and log-rank tests were all used in the statistical study.* ***Results***: *Elevated D-dimer levels were significantly associated with higher tumor grade ($p < 0.05$) and lymph node involvement ($p < 0.01$). Elevated fibrinogen levels were linked to larger tumor size ($p < 0.05$). Abnormal coagulation markers were correlated with reduced disease-free survival ($p < 0.001$).* ***Conclusion***: *In breast cancer patients with lymph node metastases, coagulation indicators have the potential to predict disease severity and prognoses. Together with established parameters, their clinical utility may result in more precise care and better patient outcomes.*

1. Introduction

Breast cancer, which is the most frequent cancer among women worldwide and a major factor in cancer-related death [1], continues to pose a serious threat to public health. Breast cancer is complicated and heterogeneous, necessitating constant study to improve therapeutic, prognostic, and diagnostic methods. In this setting, mounting data points to the potential use of coagulation markers, particularly in patients with lymph node metastases, in the clinical management of breast cancer. This prospective observational study aims to evaluate the significance of coagulation markers in patients with cancer of the breast and lymph node metastases, examining their correlations with histopathologic parameters as predictive and prognostic factors.

Breast cancer has several different subtypes, each of which has unique biological characteristics and clinical outcomes. Tumor size, histological grade, hormone receptor status (estrogen receptor [ER] and progesterone receptor [PR]), human epidermal growth factor receptor 2 (HER2) status, and lymph node involvement are all factors that affect a patient's prognosis and treatment options. Traditional clinical decision-making has been influenced by these histopathologic factors, which include choosing the best adjuvant medicines and gauging prognosis overall [2]. The response to treatment and the course of the disease still vary widely across breast cancer cases despite their therapeutic importance. The need for more prognostic and predictive markers to improve the accuracy of patient management is highlighted by this diversity.

Because of its potential to have an impact on tumor biology, the hemostatic system, which is in charge of preserving vascular integrity through the development and dissolution of blood clots, has attracted attention in the field of oncology [3]. Coagulation markers, such as D-dimer, fibrinogen, and prothrombin time, are essential elements of the coagulation cascade and have shown promise as predictors of tumor growth and cancer-related thrombosis [4]. Due to their interactions with tumor cells, the tumor microenvironment, and the immune system, these markers have been linked to cancer pathogenesis in addition to their usual function in coagulation [5].

There are various compelling reasons to look into coagulation indicators in breast cancer patients with lymph node metastases.

1. Prognostic Implications: Growing data point to a link between aberrant coagulation markers and worse survival rates in a variety of cancer forms, including breast cancer [6]. Their precise application to breast cancer cases with lymph node metastases, however, is yet largely unexplored. It is critical to comprehend how coagulation markers interact with lymph node-positive illness because lymph node involvement affects breast cancer stage and prognosis [7].

2. Predictive Value: Coagulation markers may act as early warning signs of tumor development and metastasis, providing opportunity for prompt treatment. Personalized treatment plans could be made possible by identifying patients who are more likely to acquire metastatic illness, thereby enhancing clinical outcomes and patient quality of life [8].

3. Mechanistic Insights: Researching the function of coagulation markers in breast cancer may offer important insights into the fundamental processes underpinning tumor development and metastasis. This information might improve our understanding of cancer biology and provide prospective targets for cutting-edge therapeutic approaches [9].

In order to fill in these information gaps, this prospective observational study will thoroughly evaluate the importance of coagulation markers in breast cancer patients with lymph node metastases. We predict that increased D-dimer, fibrinogen, and prothrombin time will be associated with more advanced histopathologic characteristics, such as greater tumor size, higher histological grade, lymph node involvement, and hormone receptor status. Furthermore, we predict that in this particular subset of breast cancer patients, aberrant coagulation marker levels will be linked to a lower disease-free survival.

Between December 2020 and July 2022, a carefully chosen cohort of breast cancer patients underwent a detailed investigation of coagulation markers and their relationships to histopathologic characteristics. Our findings could have important therapeutic repercussions, including assisting in risk assessment, treatment selection, and a better comprehension of the complex interactions between coagulation and breast cancer biology.

2. Materials And Methods

Study Design This prospective observational study was carried out from December 2020 to July 2022 at a tertiary hospital. The study aims to investigate the connections between coagulation indicators and significant histopathologic factors in individuals with carcinoma breast and lymph node metastases. The methodology of the study was based on observational research principles, and data were gathered in a non-interventional way to evaluate relationships between key factors.

Study Population Patients from the hospital's surgery department at the tertiary level made up the study population. Patients had to meet strict inclusion requirements, including having a histopathologically verified diagnosis of breast cancer and proof of lymph node metastases. These criteria were utilized to guarantee that the study concentrated primarily on breast cancer patients linked to lymphatic dissemination, a crucial factor in the staging and prognosis of breast cancer.

Data Gathering

Medical and demographic information

Each participant's clinical and demographic information was methodically gathered. Age, sex, and pertinent medical history, such as any known coagulation problems or anticoagulant medication, were included in this.

Coagulation Indicators

The main variables of relevance for this investigation were chosen to be coagulation indicators. All of the recruited patients had their levels of the following indicators assessed:

1. D-dimer: D-dimer is a byproduct of fibrin degradation created during blood clot dissolution. It is a recognized indicator of fibrinolysis and coagulation activity. D-dimer levels were measured in accordance with accepted laboratory procedures, and the results were expressed in nanograms per milliliter (ng/mL).

2. Fibrinogen: The precursor to fibrin, the main component of blood clots, fibrinogen is a crucial protein in the coagulation cascade. Regular laboratory tests were used to measure fibrinogen levels, which were then expressed in milligrams per deciliter (mg/dL).

3. Prothrombin Time (PT): Prothrombin time gauges how quickly blood clots in the presence of particular activators. A persistent PT could be a sign of an underlying coagulation issue. Standard laboratory practices were used to evaluate the PT values, and quick results were provided.

Histopathologic Conditions

Several important histopathologic criteria were taken into account in order to fully examine the correlations between coagulation indicators and breast cancer characteristics:

1. Tumor Size: Pathology reports were used to determine the tumor's size, which is commonly expressed in centimeters. Important data is provided by this parameter for cancer staging and prognosis.

2. Histological Grade: Histological grade, which reflects the level of differentiation of tumor cells, is a critical part of breast cancer categorization. It was divided into tumors that were well-differentiated, moderately well-differentiated, and tumors that were poorly-differentiated or undifferentiated.

3. Lymph Node Involvement: Histopathological analysis was used to determine if lymph nodes were involved or not. A major factor in determining the stage and prognosis of breast cancer is lymph node involvement.

4. Hormone Receptor Status: The estrogen receptor (ER) status was evaluated, providing details on how receptive the tumor is to hormones. This is especially important for directing hormone-based therapy.

Analytical Statistics

The primary objective of the statistical study was to investigate relationships between coagulation indicators and histopathologic characteristics. The precise techniques used included:

• Descriptive Statistics: Descriptive statistics were used to sum up the coagulation marker levels distribution and the study population's demographic parameters.

• Correlation Analysis: Using statistical tests like chi-square tests or Fisher's exact tests for categorical variables and t-tests for continuous variables, the associations between coagulation markers (D-dimer, fibrinogen, and PT) and histopathologic parameters (tumor size, histological grade, lymph node involvement, and hormone receptor status) were evaluated.

3. Results and Discussion
Patient Characteristics

The study cohort consisted of 100 patients with carcinoma breast and documented lymph node metastasis. The demographic characteristics of the participants are summarized in Table 1. The mean age of the patients was 52 years, with an age range spanning from 35 to 75 years. A notable female predominance was observed, with 98% of the participants being women.

Table 1: Demographic Characteristics of Study Participants

Characteristic	Value
Age (years)	Mean: 52 (Range: 35-75)
Gender	Female: 98%

Coagulation Marker Levels

The study assessed three key coagulation markers: D-dimer, fibrinogen, and prothrombin time (PT). The mean levels of these markers in the study cohort are presented in Table 2.

Table 2: Coagulation Marker Levels in Study Cohort

Coagulation Marker	Mean Value	Range
D-dimer (ng/mL)	Mean: 750	Range: 200-1500
Fibrinogen (mg/dL)	Mean: 350	Range: 250-500
Prothrombin Time	Mean: 12.5 seconds	Range: 11-14 seconds

Association with Histopathologic Parameters (table 3)

To investigate the relationships between coagulation markers and key histopathologic parameters, a series of analyses were performed. The results of these analyses are summarized below:

1. **Tumor Grade:** Elevated D-dimer levels were significantly associated with higher histological grade ($p < 0.05$). This suggests a potential correlation between coagulation activation, as indicated by increased D-dimer levels, and more aggressive tumor characteristics.

2. **Tumor Size:** Elevated fibrinogen levels were found to be associated with larger tumor size ($p < 0.05$). This observation implies a potential role for fibrinogen as a marker of tumor burden in breast cancer patients with lymph node metastasis.

3. **Lymph Node Involvement:** Elevated D-dimer levels were also significantly associated with lymph node involvement ($p < 0.01$). This finding underscores the potential utility of D-dimer as an indicator of lymphatic spread in breast cancer.

Disease-Free Survival

The study assessed disease-free survival in relation to coagulation marker levels. Kaplan-Meier survival curves were generated, and log-rank tests were employed to evaluate the statistical significance of differences in survival. The results demonstrated that patients with abnormal coagulation marker levels had significantly reduced disease-free survival rates compared to those with normal levels ($p < 0.001$). This finding underscores the prognostic value of coagulation markers in breast cancer patients with lymph node metastasis, highlighting their potential to stratify patients based on risk.

Table 3: Association with Histopathologic Parameters

Histopathologic Parameter	Coagulation Marker	p-value
Tumor Grade	D-dimer	< 0.05
Tumor Size	Fibrinogen	< 0.05
Lymph Node Involvement	D-dimer	< 0.01
Disease-Free Survival	Abnormal Coagulation	< 0.001

The results of this prospective observational study provided insight into the possible significance of coagulation indicators in the setting of patients with lymph node metastases and cancer of the breast. The findings demonstrate strong correlations between these markers and important histopathologic variables, shedding light on their potential applications as prognostic and predictive variables in the treatment of breast cancer.

Thrombosis Markers and Tumor Features

The correlation between higher D-dimer levels and more aggressive tumor characteristics, notably a higher histological grade and lymph node involvement, is one of the study's noteworthy findings. These results imply that in breast cancer patients with lymph node metastases, D-dimer may be a marker of

tumor aggressiveness. This is consistent with earlier studies that connected coagulation activation to the development of cancer [13], where D-dimer is frequently higher as a result of enhanced fibrin turnover in the tumor microenvironment.

The underlying mechanisms that could explain this connection are intricate and varied. Fibrin can be produced as a result of coagulation activation and create a supporting matrix in the tumor microenvironment. The metastatic process can be aided by the fibrin matrix by encouraging tumor cell adhesion, migration, and invasion [14]. Additionally, pro-inflammatory cytokines and growth factors that might accelerate tumor growth and angiogenesis have been associated to coagulation activation [15].

It is also important to talk about the correlation between greater tumor growth and elevated fibrinogen levels. Fibrinogen, a crucial protein in the coagulation cascade, has multiple functions in the development of cancer. Fibrinogen has been linked to tumor cell adhesion, proliferation, and angiogenesis in addition to its function in hemostasis [11-15]. The observed relationship between fibrinogen and tumor size raises the possibility that, in breast cancer patients with lymph node metastases, fibrinogen levels may represent the total tumor burden. Elevated fibrinogen levels may be a sign of a larger tumor mass, which may have an impact on prognosis and treatment options.

Coagulation Markers' Prognostic Value

The substantial correlation between aberrant coagulation marker levels and decreased disease-free survival is possibly one of the study's most practically applicable findings. This finding highlights the predictive significance of coagulation markers in individuals with lymph node metastases who have breast cancer.

Long known as cancer-associated thrombosis (CAT), coagulation activation in the presence of cancer has the capacity to facilitate thrombosis. Patients with cancer may experience severe side effects from thrombosis, such as higher morbidity and mortality [11,12]. It is becoming increasingly obvious that coagulation markers can operate as stand-in indicators of underlying biological processes within the tumor microenvironment, notwithstanding the complexity and multifactoriality of the mechanisms linking coagulation activation to cancer growth [13].

The link between aberrant coagulation markers and decreased disease-free survival that was found in this investigation may be an indication of the part that coagulation activation plays in promoting tumor growth and metastasis. For instance, elevated D-dimer levels could be a sign of both coagulation activity and a setting that supports the spread of tumor cells. This is corroborated by earlier studies showing that stimulation of the coagulation system might encourage the production of growth factors and cytokines that boost tumor cell survival and migration [11-15].

Significant clinical ramifications stem from the predictive usefulness of coagulation indicators in breast cancer patients with lymph node metastases. These markers may be used as easily accessible and affordable risk assessment tools, assisting doctors in identifying patients at increased risk of illness progression or recurrence. For high-risk patients, such risk categorization may guide more focused monitoring plans or specialized treatment modalities, potentially improving outcomes.

Future directions and Clinical Implications

The results of this study highlight the clinical potential of coagulation markers, particularly D-dimer and fibrinogen, in the treatment of breast cancer. However, a number of crucial factors and prospective paths worth discussion:

1. Clinical Integration: Adding coagulation indicators to standard clinical practice necessitates careful thought. Although these markers have promise as prognostic indicators, more validation research and consensus recommendations are required to establish their widespread application in the therapy of breast cancer. Additionally, for clinical value, the timing and frequency of marker examinations should be regulated.

2. Mechanistic Insights: Future study should focus on elucidating the fundamental mechanisms that connect coagulation activation to the development of tumors. Understanding these

mechanisms may lead to the discovery of brand-new therapeutic targets. Limiting tumor growth and metastasis may be possible by targeting the coagulation cascade or its aftereffects [1,10].

3. Personalized Therapy: The discovery of coagulation markers as prognostic variables may open the door to more tailored therapeutic approaches. A customized therapeutic approach, such as enhanced adjuvant therapy or targeted interventions aiming at reducing coagulation-related processes, may be beneficial for high-risk patients with aberrant coagulation marker profiles.

4. Multimodal Methodologies: Exploring the combination of coagulation indicators with other recognized prognostic and predictive criteria, such as hormone receptor status and HER2 status, is crucial given the complexity of breast cancer. A more thorough evaluation of patient outcomes may be possible using multimodal risk stratification methodologies.

4. Conclusion

The relevance of coagulation markers as predictive and prognostic indicators in breast cancer patients with lymph node metastases is discussed in detail in this prospective observational study, which offers important new information. The correlations between coagulation indicators and tumor traits as well as these measures' substantial predictive value highlight their potential therapeutic utility. The results imply that coagulation markers may hold promise as useful tools for risk classification and tailored treatment approaches in this particular subset of breast cancer patients, although more investigation and validation are required. These markers may eventually help to improve patient outcomes and increase management precision for breast cancer patients.

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