Original Article

Association of Plasma D-Dimer with Histopathological Grade and Stage of Breast Cancer

Tabassom T[1], Adhikary L[2], Saha N[3], Kabir MJ[5], Liza FA[6]

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ABSTRACT:

Background: *Breast cancer remains the most common cancer and the leading cause of cancer-related mortality among women globally. Coagulation abnormalities, including elevated plasma D-dimer levels, are frequently associated with cancer progression. Plasma D-dimer is a degradation product of fibrin and its elevation indicates increased fibrinolysis and hemostasis activation. This study evaluates the association of plasma D-dimer levels with histopathological grading and staging in breast cancer patients.*

Objective: *To assess the correlation between plasma D-dimer levels and the histopathological grade and stage of breast cancer.*

Materials and Methods: *This cross-sectional descriptive study was conducted at the Department of Pathology, Mymensingh Medical College, over a 24-month period. Venous blood samples were collected preoperatively from 86 female patients diagnosed with breast cancer. Plasma D-dimer levels were measured using immunoassays. Tumor specimens were examined histologically, graded using the Scarff-Bloom-Richardson system, and staged according to the TNM classification. Data were analyzed using SPSS software.*

Results: *The mean age of the patients was 49.57 ± 9.96 years. Plasma D-dimer levels ≥0.50 µg/ml were found in 63.9% of patients. A statistically significant increase in D-dimer levels was observed with larger tumor sizes (T1–T4). Elevated D-dimer levels were also associated with lymph node metastasis and lymphovascular invasion, but the association with histopathological grade was not statistically significant. The sensitivity and specificity of a D-dimer cutoff value of 0.52 µg/ml for predicting lymph node metastasis were 85.7% and 87.0%, respectively.*

Conclusion: *Plasma D-dimer levels were significantly associated with tumor size and lymph node involvement in breast cancer. Although there was no significant correlation with histopathological grade, elevated D-dimer levels could be a useful marker for assessing disease progression, particularly in relation to lymph node metastasis. Further studies with larger sample sizes are needed to explore its potential as a prognostic biomarker.*

Key Words: Plasma D-dimer, Breast cancer, Histopathological grade, Histopathological stage, Lymph node metastasis, Lymphovascular invasion.

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Authors:

1. Tasnova Tabassom, Assistant Professor, Department of Pathology , Netrokona Medical College, Email: tasnovatabassom78@gmail.com
2. Lovely Adhikary, Assistant Professor, Department of pathology, Ad-din Sakina Women's Medical College, Jashore, lovelymallick71@gmail.com
3. Nirjhar Saha, Assistant Professor, Mymensingh Medical College Hospital, Mymensingh, Bangladesh, Ablazeshuvo@gmail.com
4. Md. Jahidul Kabir, Lecturer, Pathology Netrokona Medical College jksayeem@gmail.com
5. Faima Amin Liza, Lecturer, Pathology, Netrokona Medical College., faimaliza@gmail.com

Correspondence:
Dr. Tasnova Tabassom, Assistant Professor, Department of Pathology , Netrokona Medical College, Email: tasnovatabassom78@gmail.com, Mobile: 01768900906

Introduction

Breast cancer (BC) is the most prevalent cancer among women worldwide, with 2.3 million new cases and 685,000 deaths in 2020 alone (World Health Organization, 2020). It accounts for 1 in 4 cancer diagnoses and 1 in 6 cancer-related deaths among women globally (GLOBOCAN, 2020). In Bangladesh, BC is the leading cause of cancer among females, with an incidence rate of 19% (WHO, 2021). Despite advancements in early detection and treatment, breast cancer remains a major cause of morbidity and mortality, particularly due to metastatic disease, which significantly worsens the prognosis (Siddiqui et al., 2021).

Histopathological grade and stage play a pivotal role in determining the prognosis and therapeutic approach for BC patients (Rakha et al. 2010). The grade of the tumor reflects its degree of differentiation, while the stage denotes the extent of tumor spread, including the size of the tumor and the involvement of lymph nodes and distant organs (Amin et al., 2017). These two factors have long been considered crucial for predicting patient outcomes and planning treatment strategies (Siddiqui et al., 2021).

In the context of breast cancer, tumor progression and metastasis are associated with an altered hemostatic system, leading to a prothrombotic state (Moik et al. 2022). Plasma D-dimer, a degradation product of fibrin, has emerged as a potential marker of fibrinolysis and global activation of hemostasis (Siddiqui et al., 2021). Elevated plasma D-dimer levels are frequently observed in cancer patients, including those with breast cancer, and have been linked with worse clinical outcomes, including lymph node metastasis and disease progression (Batschauer APB et al., 2010). Previous studies have indicated that D-dimer levels can be used as a diagnostic and prognostic tool in various cancers, including breast cancer. For example, higher plasma D-dimer levels correlate with more advanced stages of breast cancer, including larger tumor size, lymph node involvement, and distant metastasis (Lu et al., 2019; Hermansyah et al., 2022). Furthermore, D-dimer has been found to be elevated in more aggressive breast cancer subtypes, such as triple-negative breast cancer (TNBC), which is known for its poor prognosis and higher rate of metastasis (S H et al., 2018).

The rationale for this study is to investigate the association of plasma D-dimer levels with histopathological grade and stage of breast cancer, aiming to determine whether D-dimer could serve as an additional biomarker to enhance prognostic accuracy and guide therapeutic decision-making in BC patients.

Materials and Methods

This study was a cross-sectional descriptive study conducted at the Department of Pathology, Mymensingh Medical College, Bangladesh, from March 2021 to February 2023. The study aimed to evaluate the association between plasma D-dimer levels and histopathological grade and stage in breast cancer patients. A total of 86 female patients diagnosed with breast cancer were included in the study based on fine needle aspiration cytology (FNAC) or core biopsy reports. Patients with a history of chemotherapy or radiotherapy, those with other concurrent cancers, or those with conditions that affect coagulation (e.g., liver disease, pregnancy, or major trauma within the past 3 months) were excluded from the study.

After obtaining ethical approval from the Institutional Review Board (IRB) of Mymensingh Medical College, written informed consent was obtained from each participant. Preoperative venous blood samples were collected from all patients for the measurement of plasma D-dimer levels. D-dimer was quantitatively analyzed using immunoturbidimetric latex assays, a method involving monoclonal antibodies specific to the cross-linked D-dimer domain in fibrin.

Following surgical resection, tumor specimens were collected from the Department of Surgery, Mymensingh Medical College Hospital. The specimens were fixed in 10% formalin, processed, and embedded in paraffin blocks. Tumors were histologically graded using the Scarff-Bloom-Richardson grading system, which assesses tubule formation, nuclear pleomorphism, and mitotic count. Additionally, tumor staging was done using the TNM (Tumor, Node, Metastasis) staging system to assess the extent of the disease, including tumor size, lymph node involvement, and distant metastasis.

Demographic data, clinical features, and histopathological findings were recorded. Tumor characteristics such as histological grade, stage, and lymphovascular invasion

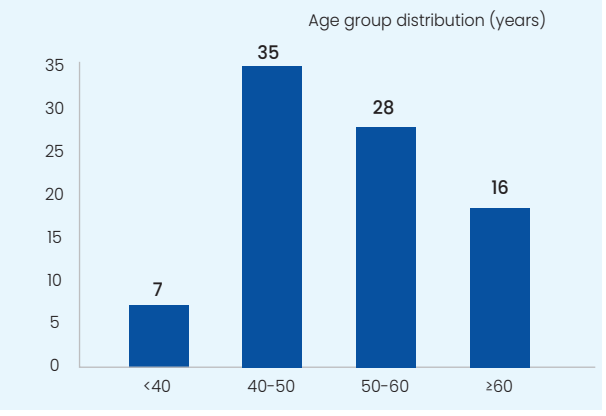
(LVI) were considered for analysis. Data were carefully checked and compiled for statistical evaluation.

Data Analysis

The collected data were analyzed using the Statistical Package for Social Sciences (SPSS) version 24. Descriptive statistics, including means, standard deviations, and percentages, were calculated for continuous and categorical variables. The relationship between plasma D-dimer levels and histopathological grade, stage, and lymphovascular invasion was assessed using chi-square tests for categorical variables. For continuous variables, t-tests and ANOVA were applied. A receiver operating characteristic (ROC) curve analysis was performed to determine the optimal plasma D-dimer cutoff value for predicting lymph node metastasis. A p-value of <0.05 was considered statistically significant.

Results

The age group distribution of the study population is depicted in Figure 1. The majority of patients (35, 40.7%) were in the 40-50 years age group, followed by 28 (32.6%) in the 50-60 years group, and 16 (18.6%) were 60 years or older. Only 7 (8.2%) patients were under 40 years of age. The mean age of the participants was 49.57 ± 9.96 years. These findings reflect a predominance of patients in the middle-aged to older age groups.



Mean ± SD = 49.57±9.96 years

Figure 1: Age group distribution of the study population (n=86)

Table 1 illustrates the distribution of plasma D-dimer levels among the studied breast cancer patients (n=86). The majority of patients had plasma D-dimer levels between 0.50-2.00 µg/mL (31.4%), followed by those with levels <0.50 µg/mL (36.1%). A smaller proportion had levels between 2.01-3.50 µg/mL (17.4%), and 15.1% of patients had levels exceeding 3.50 µg/mL. The mean plasma D-dimer level was found to be 1.73 ± 1.56 µg/mL. Normal plasma D-dimer level is considered to be <0.50 µg/mL.

Table 1: Distribution of studied patients by plasma D-dimer level (n=86)

Plasma D dimer (µg/mL)	Frequency (percentages)
<0.50	31 (36.1)
0.50-2.00	27 (31.4)
2.01-3.50	15 (17.4)
>3.50	13 (15.1)
Mean±SD 1.73±1.56	

Normal plasma D-dimer level was <0.50 µg/ml.

Table 2 presents the distribution of plasma D-dimer levels by histological grading of the studied patients (n=86). Grade I tumors had a mean D-dimer level of 0.55 ± 0.72 µg/mL, Grade II tumors had a mean of 1.72 ± 1.52 µg/mL, and Grade III tumors had a mean D-dimer level of 2.51 ± 1.82 µg/mL. A statistically significant difference in D-dimer levels was observed across the grades (p = 0.004), as determined by the ANOVA test. These findings suggest that higher plasma D-dimer levels are associated with more advanced tumor grades.

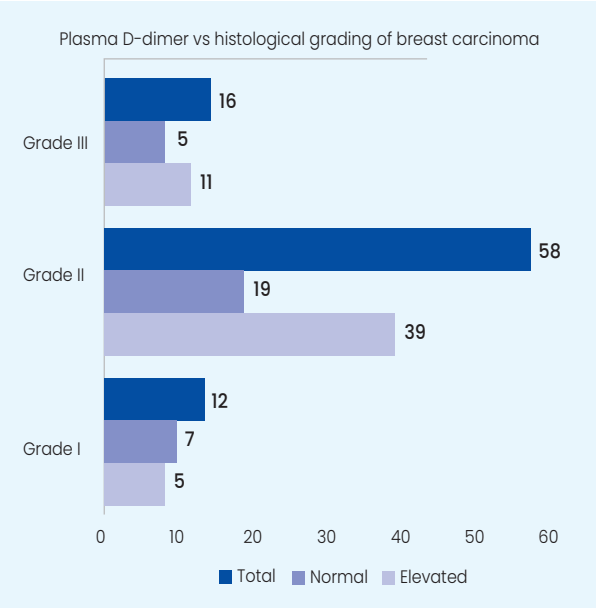
Table 2: Distribution of the studied patients and plasma D-dimer level by histological grading (n=86)

Grade	Frequency (percentages)	Mean D-dimer (µg/mL)
I	12 (14.0)	0.55±0.72
II	58 (67.4)	1.72±1.52
III	16 (18.6)	2.51±1.82
p-value		0.004

p-value reached from ANOVA test.

Figure 2 shows the association between plasma D-dimer levels and histological grading of breast carcinoma in the study population (n=86). The majority of Grade II tumors (67.4%) had elevated D-dimer levels, with 39 patients having high plasma D-dimer levels, and 19 patients exhibiting normal levels. In Grade III tumors (18.6%), 11 patients had elevated D-dimer levels, while 5 patients had normal levels. For Grade I tumors (14.0%), 7

patients had elevated D-dimer levels, and 5 had normal levels. The p-value obtained from the chi-square test was 0.221, indicating no statistically significant association between plasma D-dimer levels and histological grading.



p-value reached from chi-square test = 0.221

Figure 2: Association between plasma D-dimer and histological grading of breast carcinoma (n=86).

Table 3 shows the distribution of normal plasma D-dimer levels (<0.5 µg/mL) across different pathological stages and grades of breast carcinoma in the study population (n=31). Among the total, 7 (22.6%) patients were in Grade I, 19 (61.3%) in Grade II, and 5 (16.1%) in Grade III. The majority of patients with Grade II tumors (25.8%) had normal plasma D-dimer levels. Grade I and Grade III tumors had fewer patients with normal D-dimer levels, 9.7% and 9.7%, respectively. In Stage T1No, 3 patients were in Grade I, 8 in Grade II, and 3 in Grade III. Other stages like T2N1 and T3No had fewer patients, contributing to the overall distribution. These findings indicate variability in the presence of normal plasma D-dimer levels across tumor stages and histological grades.

Table 3: Distribution of frequency of normal plasma D-dimer level (<0.5 µg/ml) according to pathological stage and grade of breast carcinoma (n=31).

Stages (TN)	Normal plasma D-dimer level Frequency (percentages)			
	Grade I	Grade II	Grade III	Total
T1No	3 (9.7)	8 (25.8)	3 (9.7)	14 (45.2)
T1N1	1(3.2)	1 (3.2)	0 (0)	2 (6.5)
T1N2	1(3.2)	1 (3.2)	0 (0)	2 (6.5)
T2No	0 (0)	5 (16.1)	0 (0)	5 (16.1)
T2N1	2 (6.5)	1 (3.2)	2 (6.5)	5 (16.1)
T2N2	0 (0)	2 (6.5)	0 (0)	2 (6.5)
T3No	0 (0)	1 (3.2)	0 (0)	1 (3.2)
Total	07 (22.6)	19 (61.3)	05 (16.1)	31 (100)

ROC curve was performed for all possible plasma D-dimer cutoff levels with area under the curve of 0.85 (95% confidence interval of 0.75–0.95). The analysis suggested multiple cutoff points with different sensitivity and specificity rates as demonstrated in Table 4.9. The sensitivity and specificity for optimal cut off value of plasma D-dimer level (0.52 µg/mL) in present sample were found to be 85.7% and 87.0%, respectively.

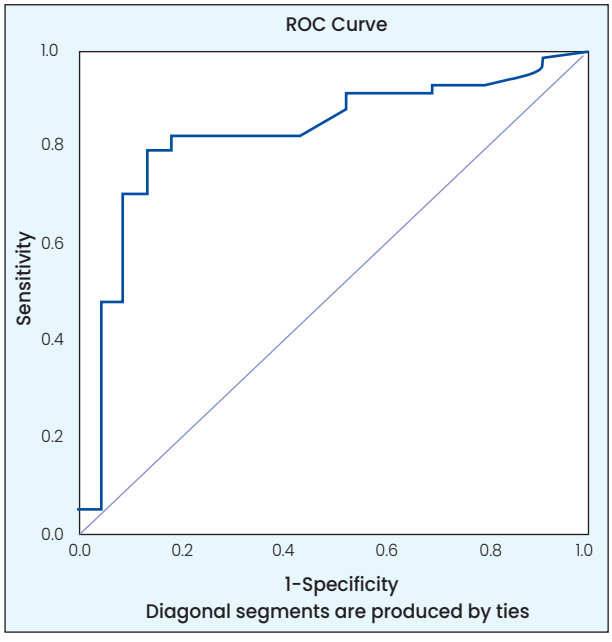


Figure 3: Receiver-Operator-Characteristics (ROC) curve for all possible D-dimer cutoff point for prediction of lymph node metastasis in breast carcinoma.

Table 4 presents the sensitivity, specificity, and Youden's J statistic for various cutoff points of plasma D-dimer levels to predict lymph node metastasis in breast carcinoma. The highest sensitivity of 98.4% and specificity of 8.7% was observed at a cutoff point of 0.10 µg/mL, while

the cutoff point of 0.52 µg/mL showed a balanced sensitivity of 85.7% and specificity of 87.0%. The Youden's J index reached its peak at a cutoff point of 0.52 µg/mL, with a value of 0.727, indicating optimal performance for predicting lymph node metastasis. These findings suggest that a plasma D-dimer level of 0.52 µg/mL is the most effective cutoff for clinical prediction of lymph node involvement.

Table 4: Sensitivity and specificity of different cutoff points of plasma D-dimer values to predict lymph node metastasis in breast carcinoma.

Cutoff point (µg/mL)	Sensitivity	Specificity	Youden's J
0.10	98.4%	8.7%	0.071
0.14	95.2%	13.0%	0.082
0.16	93.7%	22.0%	0.157
0.18	93.7%	30.4%	0.241
0.19	93.7%	47.8%	0.415
0.21	92.1%	47.8%	0.399
0.23	88.9%	52.2%	0.411
0.34	88.9%	65.2%	0.541
0.43	88.9%	78.3%	0.672
0.45	87.3%	78.3%	0.656
0.47	85.7%	79.3%	0.650
0.49	85.7%	82.6%	0.683
0.52	85.7%	87.0%	0.727
0.61	82.5%	87.0%	0.695
0.81	79.4%	87.0%	0.664

Discussion

Breast cancer remains the most common malignancy among women worldwide, with a significant impact on morbidity and mortality. Despite advancements in early detection and treatment, metastasis remains a leading cause of poor prognosis. Histopathological grade and stage are key determinants of prognosis and therapeutic approaches in breast cancer patients (Rakha et al., 2010). However, emerging biomarkers like plasma D-dimer, a marker of fibrinolysis and coagulation, are increasingly being explored to improve disease monitoring and prediction of clinical outcomes.

Our study demonstrated a significant association between elevated plasma D-dimer levels and larger tumor sizes, as well as lymph node involvement, which is consistent with previous studies (Siddiqui et al., 2021; Hermansyah et al., 2022). The correlation between plasma D-dimer levels and tumor stage further supports the idea that D-dimer could serve as a non-invasive biomarker to monitor disease progression and metastasis (Lu et al., 2019; Moik et al., 2022). Plasma D-dimer levels were significantly higher in patients with larger tumors (T3 and T4) and more extensive lymph node metastasis, reinforcing findings from earlier studies indicating that tumor progression activates the coagulation cascade (Batschauer et al., 2010; Siddiqui et al., 2021).

Interestingly, while elevated D-dimer levels were associated with tumor size and lymph node involvement, no significant correlation was observed with histopathological grade in our study. Previous studies have also shown mixed results regarding the relationship between D-dimer levels and tumor grade. For instance, some studies have reported a positive correlation between D-dimer levels and high-grade tumors (S H et al., 2018; Hermansyah et al., 2022), while others have not (Lu et al., 2019). The lack of significance in our study could be attributed to the sample size, as larger multicenter studies may offer more comprehensive insights into this relationship.

Moreover, our study highlighted the predictive value of plasma D-dimer for lymph node metastasis, with an optimal cutoff value of 0.52 µg/mL. This cutoff demonstrated high sensitivity (85.7%) and specificity (87.0%), which aligns with findings from other studies that have underscored the utility of D-dimer as a reliable marker for metastasis (Lu et al., 2019). The receiver operating characteristic (ROC) analysis in our study further supports the idea that D-dimer can help stratify patients at high risk of metastasis, potentially aiding in decision-making for aggressive therapies. In addition, elevated D-dimer levels have been shown to correlate with poor prognosis in breast cancer patients, especially those with aggressive subtypes such as triple-negative breast cancer (TNBC). This aligns with findings from other studies that link elevated D-dimer levels with poor clinical outcomes and higher rates of metastasis in TNBC (Siddiqui et al., 2021). Our results also echo findings from a study by S H et al. (2018), who observed that high plasma D-dimer levels were significantly associated with lymph node involvement and higher histopathological grade.

While D-dimer has shown promise as a prognostic biomarker, it is important to note that it should not be

considered in isolation. The combination of plasma D-dimer levels with traditional histopathological grading and staging could enhance the overall prognostic accuracy and guide treatment decisions. Our study suggests that plasma D-dimer, when combined with histological grade and stage, can provide a more comprehensive understanding of disease progression and metastatic risk (Moik et al., 2022).

In conclusion, plasma D-dimer levels represent a promising biomarker for assessing tumor size, lymph node metastasis, and overall disease progression in breast cancer patients. Further studies with larger sample sizes and multicenter data are necessary to validate its role in clinical practice and refine cutoff values for predicting metastasis.

Conclusion

plasma D-dimer levels are significantly associated with tumor size and lymph node involvement in breast cancer. Although no significant correlation was found with histopathological grade, elevated D-dimer levels could serve as a useful prognostic biomarker for disease progression. Further studies with larger sample sizes are needed to validate its clinical utility. Plasma D-dimer may complement traditional grading and staging systems in predicting patient outcomes.

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