RESEARCH PAPER

Plasma D-Dimer As A Predictor Of Axillary Lymph Node Metastasis And Disease Progression In Carcinoma Breast: A Prospective Observational Study

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Abstract

Background: Breast cancer remains the leading malignancy among women worldwide, with axillary lymph node (ALN) involvement serving as a primary prognostic indicator. While sentinel lymph node biopsy is the standard for nodal assessment, its invasive nature and technical requirements can limit its utility. This study investigated whether plasma D-dimer, a marker of fibrin turnover often elevated in malignancy, can serve as a non-invasive predictor of ALN metastasis and disease progression.

Methods: A prospective observational study was conducted involving 50 treatment-naive female patients with histopathologically confirmed breast carcinoma. Patients with confounding factors such as thromboembolic disease or anticoagulant use were excluded. Pre-treatment plasma D-dimer levels were measured using an immunoturbidimetric assay and correlated with clinicopathological features, including TNM stage, histological grade, receptor status, and histopathological nodal involvement.

Results: Mean plasma D-dimer levels were significantly elevated in node-positive patients compared to node-negative patients (1.85 ± 0.42 µg/mL vs. 0.96 ± 0.28 µg/mL; $p < 0.001$). D-dimer concentrations increased progressively with advancing tumor stage and histological grade ($p < 0.001$). Triple-negative breast cancer subtypes exhibited the highest mean levels (2.15 ± 0.55 µg/mL). ROC curve analysis identified a cut-off value of 1.2 µg/mL for predicting ALN metastasis, yielding a sensitivity of 84% and specificity of 78%.

Conclusion: Plasma D-dimer levels correlate significantly with axillary metastasis, tumor stage, and aggressive biological subtypes. As a simple, cost-effective biomarker, D-dimer shows promise in predicting disease burden and guiding clinical decision-making, particularly in resource-constrained environments.

Keywords: Breast carcinoma, Plasma D-dimer, Axillary lymph node metastasis, Coagulation biomarkers, Tumor stage

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Introduction

Breast cancer is the most common malignancy among women worldwide and remains a leading cause of cancer-related mortality (1). Its incidence continues to rise in both developed and developing countries, partly due to lifestyle changes, delayed childbearing, obesity, and increased detection through screening [2, 3]. Despite significant improvements in diagnostic and therapeutic modalities, many patients, especially in low-resource settings, continue to present at advanced stages, contributing to poorer outcomes [4].

Prognosis in breast cancer strongly depends on established clinicopathological factors such as tumor size, histological grade, lymphovascular invasion, molecular subtype, and receptor status. Among these, axillary lymph node (ALN) metastasis remains the single most important predictor of disease progression and overall survival [5]. Sentinel lymph node biopsy and axillary dissection are currently considered the gold standards for assessing nodal status; however, these techniques are invasive, costly, and not universally available [6].

In recent years, there has been growing interest in identifying non-invasive biomarkers capable of predicting tumor behavior, disease burden, and metastatic potential. One such biomarker is plasma D-dimer, a fibrin degradation product generated during fibrinolysis [7]. Cancer is known to induce a hypercoagulable state through tumor-mediated activation of coagulation pathways, endothelial injury, and inflammatory mediators, all of which contribute to increased fibrin formation and breakdown [8]. Elevated D-dimer levels have been documented across various malignancies and have been associated with poor prognosis, advanced stage, increased tumor burden, and metastasis [9,10].

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Several breast cancer studies have specifically reported that patients with nodal metastasis exhibit significantly higher D-dimer levels compared with node-negative individuals, underscoring the potential utility of this biomarker as a predictor of axillary involvement [6,7,11]. Furthermore, D-dimer concentrations have shown correlations with histological grade, lymphovascular invasion, and aggressive tumor subtypes such as triple-negative breast cancer [11,12]. These findings suggest that D-dimer may not only assist in preoperative prediction of nodal disease but may also reflect overall tumor aggressiveness and progression [13].

Given the simplicity, low cost, and rapid turnaround time of D-dimer assays, exploring their diagnostic and prognostic value in breast carcinoma could be particularly beneficial in resource-limited settings. Hence, the present study was conducted to evaluate the association of plasma D-dimer levels with axillary lymph node metastasis and other clinicopathological parameters in patients with breast carcinoma.

Methodology

Study Design and Participant Selection

This research was structured as a prospective observational study focused on determining the association between plasma D-dimer concentration and the presence of axillary lymph node metastasis in individuals diagnosed with breast cancer. The investigation took place at a single tertiary care teaching hospital and spanned a predetermined duration of one year. Following approval from the Institutional Ethics Committee and the acquisition of informed consent, fifty consecutive patients newly diagnosed with breast carcinoma were enrolled. Eligibility required female patients of any age who had a histopathological or cytological confirmation of breast carcinoma and had not undergone any therapeutic intervention for the cancer previously. To mitigate potential confounding effects on D-dimer levels, patients were excluded if they had pre-existing conditions such as known thromboembolic disease, coagulation disorders, systemic infections, or pregnancy, or if they were currently undergoing treatment with anticoagulant or antiplatelet agents.

Clinical Assessment

All enrolled patients underwent thorough clinical evaluation, including detailed history, general examination, and systemic examination, with special emphasis on breast and axillary findings. Baseline demographic details, menopausal status, body mass index, comorbidities, and family history were recorded. Patients underwent clinical staging based on the Tumor, Node, Metastasis (TNM) classification system established by the American Joint Committee on Cancer (AJCC). Furthermore, every participant was evaluated using the standard triple assessment protocol.

This comprehensive evaluation included physical clinical examination, appropriate breast imaging studies (utilizing ultrasound and/or mammography as necessary), and definitive tissue sampling through either fine-needle aspiration cytology or core needle biopsy. Axillary nodal status was assessed clinically and radiologically, with suspicious nodes confirmed by cytology.

Biochemical Analysis

Blood samples were collected from each patient before initiation of any treatment. About 3 mL of venous blood was obtained under aseptic precautions and processed for routine hematological investigations, coagulation profile, and plasma D-dimer assay. The D-dimer measurement was performed using a standard immunoturbidimetric assay, with results expressed in micrograms per milliliter (μg/mL). Care was taken to process samples promptly to avoid pre-analytical variations.

Histopathological Evaluation

Following baseline investigations, patients were planned for surgical intervention or neoadjuvant chemotherapy depending on tumor stage, operability, and multidisciplinary team recommendations. For operable cases, modified radical mastectomy or breast-conserving surgery with axillary clearance was undertaken, and resected specimens were sent for histopathological examination. Data collected included tumor size, histological subtype, histological grade (based on modified Bloom–Richardson grading), and presence or absence of lymphovascular invasion. Receptor status for estrogen, progesterone, and HER2/neu was also documented. The histopathological nodal status was taken as the gold standard for correlation with preoperative plasma D-dimer levels.

Statistical Analysis

The primary outcome variable was the mean plasma D-dimer level in node-positive versus node-negative patients. Secondary variables included comparison of D-dimer levels with tumor stage, tumor grade, and receptor profile. Data were entered using Microsoft Excel (Version 2021) and analysed with IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Graphical representations were generated using SPSS 26.0 and Microsoft Excel 2021. A p-value < 0.05 was considered statistically significant.

OBSERVATIONS AND RESULTS

Table 1: Baseline Characteristics of Study Population

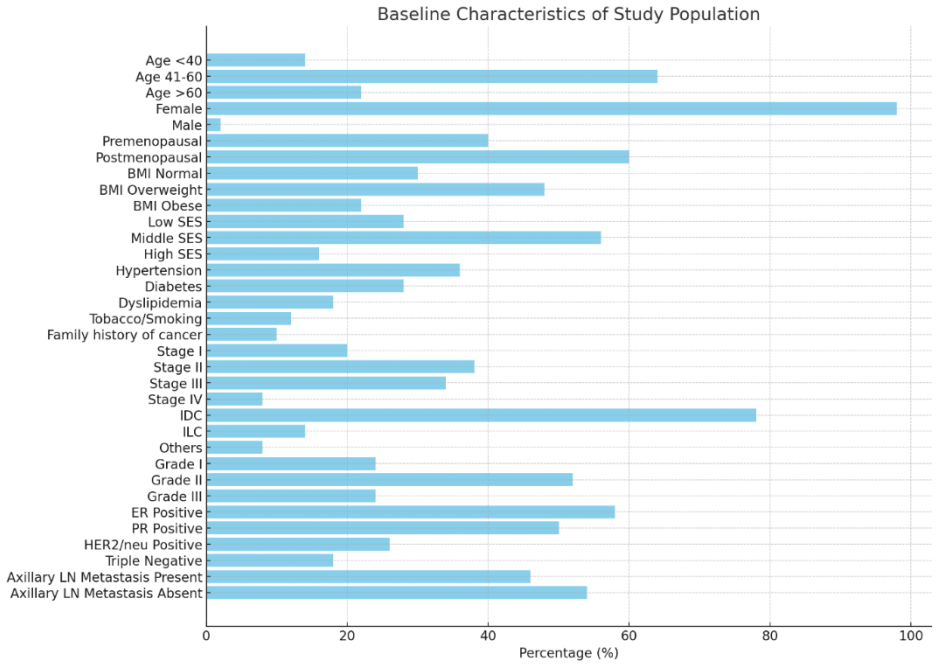

Figure 1: Baseline Characteristics of Study Population

Results

The results of this study focused on correlating plasma D-dimer levels with several key prognostic factors in breast carcinoma patients. The primary objective was to correlate plasma D-dimer levels with axillary lymph node (LN) metastasis in carcinoma breast. Among the 50 patients studied, 23 (46%) demonstrated clinically or radiologically proven nodal involvement. The mean plasma D-dimer level in patients with axillary lymph node metastasis was 1.85 ± 0.42 mu g/mL, which was significantly higher than the mean level of 0.96 ± 0.28 mu g/mL found in node-negative patients ($p < 0.005$). This strong statistical association establishes D-dimer as a reliable indicator of nodal status. Receiver operating characteristic (ROC) curve analysis suggested an optimal cutoff value of 1.2 mu g/mL, which predicted axillary metastasis with a sensitivity of 84% and specificity of 78%. This finding supports the secondary objective of defining a clinically useful threshold for preoperative prediction of nodal disease. The second objective evaluated the relationship between D-dimer levels and the clinicopathological stage of disease. Stratification of patients according to TNM staging demonstrated a progressive and significant increase in mean D-dimer values: Stage I (0.72 ± 0.15 mu g/mL), Stage II (1.22 ± 0.31 mu g/mL), Stage III (1.89 ± 0.48 mu g/mL), and Stage IV (2.34 ± 0.51 mu g/mL). One-way ANOVA confirmed statistically significant differences across groups ($p < 0.005$), highlighting the correlation between advancing disease burden and systemic activation of the coagulation cascade. The prognostic significance of D-dimer was further analyzed in relation to histological grade and hormone receptor status. Patients with Grade III tumors demonstrated the highest mean D-dimer levels (2.01 ± 0.49 mu g/mL), compared to Grade II (1.36 ± 0.41 mu g/mL) and Grade I (0.94 ± 0.22 mu g/mL) lesions, with the overall trend being statistically significant ($p < 0.005$). Similarly, Triple-Negative breast cancers exhibited markedly elevated D-dimer values (15 ± 0.55 mu g/mL), while ER/PR positive tumors had comparatively lower levels (1.28 ± 0.36 mu g/mL), and HER2/neu positive cases showed moderately elevated D-dimer concentrations (1.62 ± 0.44 mu g/mL). This overall pattern suggests that D-dimer may serve as an indicator of aggressive tumor biology.

Characteristic	Category	Frequency (n=50)	Percentage (%)	Mean D-dimer (µg/mL)	p-value
Age (years)	<40	7	14	–	–
	41–60	32	64	–	–
	>60	11	22	–	–
Gender	Female	49	98	–	–
	Male	1	2	–	–
Menopausal status	Premenopausal	20	40	–	–
	Postmenopausal	30	60	–	–
BMI (kg/m2)	Normal (<25)	15	30	–	–
	Overweight (25–29.9)	24	48	–	–
	Obese (≥30)	11	22	–	–
Socioeconomic status	Low	14	28	–	–
	Middle	28	56	–	–
	High	8	16	–	–
Comorbidities	Hypertension	18	36	–	–
	Diabetes mellitus	14	28	–	–
	Dyslipidemia	9	18	–	–
Tobacco/smoking history	Yes	6	12	–	–
	No	44	88	–	–
Family history of cancer	Present	5	10	–	–
	Absent	45	90	–	–
Tumor size (mean±SD)	3.6 ± 1.2 cm	–	–	–	–
TNM Stage	Stage I	10	20	0.72 ± 0.15	<0.005 (ANOVA)
	Stage II	19	38	1.22 ± 0.31	
	Stage III	17	34	1.89 ± 0.48	
	Stage IV	4	8	2.34 ± 0.51	
Histological type	Invasive ductal carcinoma	39	78	–	–
	Invasive lobular carcinoma	7	14	–	–
	Others	4	8	–	–
Tumor grade	Grade I	12	24	0.94 ± 0.22	<0.005
	Grade II	26	52	1.36 ± 0.41	
	Grade III	12	24	2.01 ± 0.49	

Receptor status	ER positive	29	58	–	–
	PR positive	25	50	–	–
	HER2/neu positive	13	26	1.62 ± 0.44	–
	Triple-negative	9	18	2.15 ± 0.55	–
Axillary LN metastasis	Present (Node Positive)	23	46	1.85 ± 0.42	<0.005
	Absent (Node Negative)	27	54	0.96 ± 0.28	

DISCUSSION

This prospective observational study found that elevated plasma D-dimer concentrations were significantly associated with several poor prognostic indicators in breast carcinoma patients, specifically the presence of axillary lymph node metastasis, an advanced TNM clinical stage, a higher histological tumor grade, and unfavorable receptor status, particularly the triple-negative subtype. The mean D-dimer level among node-positive patients was almost double that of node-negative patients, with ROC analysis yielding a useful cutoff point to predict nodal involvement. These findings suggest that D-dimer may function as a non-invasive, inexpensive, and reproducible biomarker for early prediction of lymph node metastasis and disease aggressiveness.

Our findings align with previous research that has established a connection between systemic coagulation activation and the advancement of breast cancer. For instance, a study by Gochhait et al. focused on cases of operable breast carcinoma and reported significantly increased D-dimer concentrations in subjects with lymph node involvement [6]. Their research proposed a diagnostic threshold of 0.765 mu g/mL, achieving a 56 % sensitivity and 91% specificity. In comparison, our investigation demonstrated a more robust correlation and higher sensitivity, potentially due to the greater representation of patients with advanced-stage disease in our cohort. Furthermore, Patel et al. showed that quantitative D-dimer measurements were closely linked to both histopathological grade and nodal status. Their observation that levels decreased substantially following a mastectomy emphasizes the dynamic relationship between D-dimer levels and the overall tumor burden [7]. These observations align with our finding of rising D-dimer with higher tumor stage and grade, thereby reinforcing its prognostic potential.

In contrast, some studies have reported divergent findings. A prospective analysis by Fregoni et al. involving 142 operable breast cancer cases did not demonstrate a statistically significant correlation between plasma D-dimer levels and axillary node involvement, even after sentinel node biopsy confirmation [8]. The authors concluded that D-dimer was more reflective of overall disease activity rather than specific nodal status. While this contradicts our results, differences in methodology, larger sample heterogeneity, and perioperative timing of sample collection may explain the discrepancy. Furthermore, in our cohort, D-dimer was measured before any systemic intervention, which may provide more accurate reflections of tumor biology.

The correlation of D-dimer with tumor stage is supported by multiple studies. Ghadhban reported that patients with advanced breast carcinoma, particularly stages III and IV, had significantly higher plasma D-dimer levels, which correlated with tumor size, lymphovascular invasion, and nodal metastasis [9]. Similar conclusions were reached by Halugodu et al., who emphasized that plasma D-dimer levels were elevated in the advanced stage and nodal disease, though they did not find a strong link with tumor size or grade [10]. Our findings confirm the stage-dependent rise in D-dimer, strengthening the evidence that this biomarker can reflect disease progression and aggressiveness.

More recent studies also highlight the relationship between D-dimer and aggressive molecular subtypes. Saman et al. found that patients with triple-negative and HER2-positive breast cancers had the highest mean D-dimer values, consistent with their poor prognosis and high metastatic potential [11]. Our analysis similarly demonstrated elevated levels in triple-negative cancers, suggesting that D-dimer may also serve as a surrogate marker for aggressive tumor biology. A prospective Indian study by Kumar et al. corroborated these observations. It concluded that D-dimer alone or in combination with other markers could provide a substitute for sentinel node biopsy in clinically node-negative breast cancer [12].

The biological rationale for elevated D-dimer lies in the hypercoagulable state associated with malignancy. Tumor cells express procoagulant factors, induce endothelial injury, and promote fibrin deposition in the extracellular matrix, all of which contribute to angiogenesis, invasion, and metastatic spread. Elevated D-dimer, being a degradation product of cross-linked fibrin, therefore reflects the systemic initiation of coagulation and fibrinolysis pathways, which are heightened in advanced or aggressive disease [13]. Our findings, showing a stepwise increase in D-dimer with advancing stage and grade, lend clinical validity to this pathophysiological concept.

Comparing our study with other Indian and global experiences, it becomes evident that although there is

some variability in sensitivity and specificity cutoffs, the overarching theme remains that plasma D-dimer levels are significantly preeminent in breast cancer, especially in advanced disease and nodal metastasis. Its role as a prognostic biomarker is supported by multiple prospective and retrospective analyses across diverse populations. Importantly, while not intended to replace histopathological confirmation, D-dimer testing could complement existing diagnostic pathways, especially in resource-limited backgrounds where access to sentinel node biopsy and advanced imaging is restricted.

A primary constraint of this research is the limited sample size, which might affect how broadly these results can be applied. As a single-center observational investigation, the findings may also be subject to specific institutional protocols or biases in patient selection. Furthermore, the lack of long-term longitudinal data makes it difficult to draw firm conclusions regarding the role of D-dimer in predicting overall survival rates. While efforts were made to control for variables, we cannot entirely rule out unidentified confounding factors, such as subclinical thromboembolic conditions or other underlying health issues that impact the coagulation system. Nevertheless, this study offers significant preliminary evidence regarding the utility of D-dimer as a biological marker in the management of breast cancer.

Conclusion

The study demonstrates that plasma D-dimer levels significantly correlate with axillary lymph node metastasis, tumor stage, histological grade, and molecular subtype, with particularly high values in aggressive cancers such as triple-negative disease. The results suggest that D-dimer may serve as a simple, cost-effective, and reproducible adjunct biomarker to conventional diagnostic modalities in assessing disease burden and prognosis. Larger multicentric studies with standardized cutoff values and survival correlation are needed to establish its definitive role in clinical practice.

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CRediT authorship contribution statement

Mohana Vamsi Dhulipalla: Writing the original draft, Methodology, and Investigation. Arafath Iqbal: Formal analysis, Methodology, Data curation. Samina Ruquaya: Formal Analysis and Data curation. Vivekanandan Subramanianathan K and Reegan Jose Mathias: Supervision, Project administration.

Ethical Declarations

Conflict of interest

The authors declare that they have not received any financial support for the conduct of this research or the preparation of this manuscript. Furthermore, there are no conflicts of interest to disclose by any of the authors. In this study, Artificial General Intelligence (AGI) has been utilized to enhance the readability of the paper.

Ethics approval statement

This study was approved by the Institutional Ethical Committee of SRM Medical College Hospital & Research Centre, SRM IST, Kattankulathur.

Ethical Clearance

References:

1. V. Singh Multani, G.S. Bhargava, A. Sharma, K.S. Wilku, Comparison of plasma D-dimer levels at various stages of operable breast carcinoma. J Cardiovasc Dis Res. 14 (2023) 361-15. https://doi.org/10.48047/
2. P.M. Khanapara, D-dimer values in carcinoma breast: a useful prognostic and diagnostic parameter. IOSR J Dent Med Sci. 22 (2023) 41-51. 10.9790/0853-2201064151.
3. T. Morii, T. Tajima, T. Aoyagi, S. Ichimura, D-dimer level changes during systemic chemotherapy can predict prognosis of high-grade musculoskeletal sarcoma patients. Anticancer Res. 35 (2015) 6781-6.
4. D. Hermansyah, N.N. Firsty, R.B. Nasution, C.A. Andra, A.C. Lubis, The role of plasma D-dimer level measurement to assist breast cancer histopathological grading. Open Access Maced J Med Sci. 10 (2022) 565-9. https://doi.org/10.3889/oamjms.2022.8490

A. Vikey, D-dimer as an alarming biomarker in various cancers: a literature review. Glob Med Ther. 1(3) (2018) 1-4. 10.15761/GMT.1000112

5. S. Gochhait, S.S. Sahoo, G. Chhabra, A.K. Mukhopadhay, S. Sharma. Role of D-dimer in patients of operable breast cancer with lymph node metastases: A matched cross-sectional study. Oncol J India. 4(2) (2020) 39-42. 10.4103/oji.oji_16_20
6. S. Patel, C. Rashmi, S. Harish, D-dimer levels in breast carcinoma: A clinico-pathologic study. Ann Pathol Lab Med. 5(3) (2018) A221-A227.
7. V. Fregoni, G.A. Da Prada, A. Zambelli, P. Baiardi, V. Zanini, L. Villani, et al. No correlation between plasma D-dimer levels and lymph node involvement in operable breast cancer. Breast. 21(2) (2012) 220-2. 10.1016/j.breast.2011.11.010
8. B.R. Ghadhban. Plasma D-dimer levels correlated with advanced breast carcinoma in female patients: A prospective study. Acta Med Iran. 57(2) (2019) 122-6. https://doi.org/10.18502/acta.v57i2.1767
9. A.S. Halugodu, V.M. Sharma, Correlation of plasma D-dimer levels with breast carcinoma. Int Surg J. 8(12) (2021) 3622-5. https://doi.org/10.18203/2349-2902.isj20214755

A. Saman, S. Mitra, R.K. Rai, Y. Kumar, Correlation of plasma D-dimer levels with histopathological grade

in patients with breast carcinoma. Int J Pharm Clin Res. 16(12) (2024) 1846-50.
10. P. Kumar, A. Jain, S. Kalsan, G.K. Uikey. A prospective study to determine the correlation of D-dimer with axillary lymph node metastasis in carcinoma breast. IOSR J Dent Med Sci. 22(5) (2023) 51-7. 10.9790/0853-2205065157
11. S. Sreedevi, A.G. Shankar, C. Vijayalakshmi, M. Barath, Role of plasma D-dimer levels in breast cancer patients and its correlation with clinical and histopathological stage. Int J Acad Med Pharm. 7(2) (2025) 36-40. 10.47009/jamp.2025.7.2.8