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PLASMA D-DIMER LEVELS IN BREAST CANCER PATIENTS – A PROSPECTIVE STUDY IN A TERTIARY CARE CENTRE.

Dr. Renukadevi Vadivelu*	Junior Resident Department Of General Surgery Sree Mookambika Institute Of Medical Sciences *Corresponding Author
Dr. Eedara Sri Kousalya	Junior Resident Department Of General Surgery Sree Mookambika Institute Of Medical Sciences
Dr. S. Jaya Sakthi	Senior Resident Department Of General Surgery Sree Mookambika Institute Of Medical Sciences.

ABSTRACT

Background: Breast cancer, the most common female cancer, is a heterogeneous group of tumours with varying behaviours and responses to therapy. Complex and micro-level modifications of the host's coagulation function may occur at some time because the responsiveness of the tumour cells byproduct will dysregulate its physiologic function, as reflected by a higher rate of fibrinolysis, which will increase the D-dimer level. **Aim:** To evaluate the role of D-dimer in patients of carcinoma breast and to determine the relationship with clinical and histopathologic parameters. **Materials And Method:** The present study was a cross sectional study conducted for a period of one year from march 2022 to February 2023. The patients admitted in Department of General Surgery with FNAC/trucut biopsy proven operable carcinoma breast during the study period were included in the present study. A total of 47 patients were recruited. Peripheral venous blood was collected and analyzed D-dimer levels. Normal range of D Dimer was <0.5 mg/L or <500ng/ml. Modified radical mastectomy done for the all the patients. Post-operative histopathology report for lymphovascular invasion, tumor stage, grade of carcinoma breast was compared to d-dimer levels. Results were analysed using SPSS 20.0 version and the association was tested using Chi square test. **Results:** The age of patients ranged from 37-63 years with mean age of 51.9 years and majority 19(40.42%) of the patients were in the age group of 51 to 60 years. Among the 47 patients 38(%) had D dimer value more than 0.5 mg/L. When the histological grade of the disease was compared, D-dimer levels increased with increasing grade (p=0.024). D-dimer levels increased with tumour size (p<0.001), presence of lymph node involvement (p=0.039), lymphovascular invasion (p=0.047), and clinical stage (p0.001). **Conclusion:** Plasma D-Dimer levels are higher in breast cancer, particularly in advanced stages. D-Dimer levels that are elevated are important indicators of clinical stage, lymphovascular invasion, lymph node involvement, and clinical stage. As a result, preoperative Plasma D-Dimer could be a safe, simple, and easily accessible prognostic marker of advanced breast cancer.

KEYWORDS : Breast carcinoma, Biopsy, D dimer, lymphovascular invasion, Tumor stage,

INTRODUCTION:

Breast cancer is the most prevalent malignant neoplasm in women and comprises a diverse group of tumours with varying behaviours and responses to therapy. Breast cancer is the most frequent malignancy in women and one of the leading causes of mortality among them.[1] Breast cancer is becoming more widespread in India, and it is now the second most common malignancy after cervical cancer. Biological markers, histological grading and subgroup status, tumour size, hormonal status, and lymph node involvemant all have predictive and/or prognostic value and are essential considerations in determining the best treatment.[2]

Malignancy and thrombosis have been linked for more than a century. The intricate interaction of tumour cells and their byproducts with host cells results in varying degrees of compromise of the host's natural defence mechanisms, which normally protect it from thrombogenesis, which causes the hypercoagulable scenario in malignancy. The blood clotting cascade can be directly activated by tumour cells, leading to thrombosis, or they can generate procoagulant properties while inhibiting those of vascular endothelial cells, platelets, monocytes, and macrophages.[3]

An essential first stage in tumour metastasis is the deposition and remodelling of fibrin in the extracellular matrix of the tumour. For both tumour cell migration during invasion and endothelial cell movement during angiogenesis, cross-linked fibrin in the extracellular matrix provides a sturdy framework.[4] Thrombocytosis, an upsurge in fibrinogen and fibrin breakdown products such D-dimer, an increase in factors V, VII, VIII, IX, and XI levels, along with a decrease in antithrombin III levels have all been documented in cancer patients.[5]

D dimer has a long history of being linked to many cancers as well as other illnesses like deep vein thrombosis and venous thromboembolism. Trousseau was the one to first note an increase in coagulopathies in cancer patients.[6] The presence of D dimer is a sensitive marker of elevated fibrinolytic activity in cancer patients. D dimer assessment is an effort to use a specific marker to assess the severity of the disease in people with breast cancer. It uses a product of fibrin degradation called a D dimer. During fibrinolysis, the disintegration of cross-linked fibrin results in the formation of D-dimer molecules.[7]

The major cause of death in breast cancer patients is still the development of distant metastases. In patients with infiltrative breast cancer, the presence of metastases in the axillary lymph nodes is a significant prognostic indicator of survival. Elevated plasma d-dimer is associated and correlated with distant metastases, axillary lymph node metastasis, or locally advanced breast cancer.[8]

Various studies have been conducted to support this finding, with fibrinolytic activity associated with elevated D dimer levels in breast cancer patients. This study sought to assess the role of D-dimer in the prediction of lymph node metastasis in carcinoma patients, as well as the relationship of these markers with histopathologic parameters known to have predictive and prognostic value in carcinoma breast.

MATERIALS AND METHODS:

The present study was a cross sectional study conducted in Department of General Surgery, Sree Mookambika Institute of Medical Sciences, Kulasekharam for a period of one year from March 2022 to February 2023. The patients admitted in Department of General Surgery with FNAC/trucut biopsy

proven operable carcinoma breast during the study period were included in the present study. Patients with other malignancies, comorbidities like myocardial infarction, cerebrovascular disease, coagulation/ bleeding disorders, recent history or presence of infection, pregnant women, smokers, on oral contraceptive pills and patients not willing to participate in the presents study were excluded. A total of 47 patients were recruited.

Peripheral venous blood was collected pre-operatively and analyzed D-dimer levels. the value of >0.5 mg/L or >500ng/ml was presumed as an elevated D-dimer level. The immunoassays were used to identify the D-dimer domain in fibrinogen, which is specifically expressed by monoclonal antibodies. Clinical staging was performed, taking into account TNM, tumour size, nodal involvement and metastasis. All patients underwent modified radical mastectomy. Lymph node involvement, lymphovascular invasion, and histological grade by Modified Bloom Richardson (MBR) were taken into consideration while grading the disease. A comparison between d-dimer levels and the post-operative histopathology report for lymphovascular invasion, tumour stage, and grade of breast cancer was made.

Data entered in Excel sheet. Results were analysed using SPSS 20.0 version. The categorical data were represented as n (%) and numerical data in mean standard deviation. Unpaired 't' test was used to compare the mean between the normal and microalbuminuria groups. Chi square test was used to determine the strength of association between different variables. A p value less than 0,05 was considered statistically significant.

OBSERVATION AND RESULTS:

All patients were enrolled in our study were females. The age of patients ranged from 37-63 years with mean age of 51.9 years and majority 19(40.42%) of the patients were in the age group of 51 to 60 years. Among the 47 patients 19(%) had D dimer value between 2 to 5 mg/L. (Table 1)

Table 1: Distribution of D dimer values

D Dimer (mg/L)	N(%)
<0.5	12(25.53%)
0.5-2	8(17.02%)
2-5	18(38.3%)
>5	9(19.15%)

When histological grade of the disease was compared, there was an elevation of D-dimer levels with increase in the grade. Grade I showed least mean value while grade III showed maximum value (Table 2). This increase showed statistically significance.

Table 2: Comparison of mean D dimer values with histological grade

Histological (MBR) grade	N (%)	Mean D- dimer (mg/L)	p value
I	6(12.77%)	0.84	0.029
II	23(48.93%)	2.12	
III	18(38.3%)	5.4	

An increase in D-dimer levels was noted with increase in tumor size, all the tumor in T3 and T4 showed elevated D dimer levels (p<0.001). Histopathological report revealed 36 out of 47 patients showed involvement of axillary lymph nodes with an elevated D-dimer level. The rise in plasma D-dimer was statistically significant with p value of 0.039.

On histological examination, patients with lymphovascular invasion had higher mean plasma D-dimer values compared to patients without lymphovascular invasion, 3.75 and 0.21, respectively (p = 0.047), and this was statistically significant (p=0.004) (Table 3). Patients with cancer in stages I and II had mean D-dimer levels that were less than 0.5 mg/L, but patients with cancer in stages III and IV had higher mean D-dimer values. Furthermore, the rise was determined to be statistically significant, with a p value less than 0.001.

Table 4: Comparison of D dimer values with tumor size, lymph node involvement and lymphovascular invasion

Parameters		D-dimer (mg/L)		Mean D-dimer (mg/L)	p-value
		<0.5	>0.5		
Tumor size	T1	8(66.67%)	1(2.86%)	0.35	<0.001
	T2	4(33.33%)	8(22.86%)	0.72	
	T3	0(0%)	15(42.85%)	2.42	
	T4	0(0%)	11(31.43%)	4.68	
Lymph nodes involved	Involved	3(25%)	32(91.43%)	3.93	0.039
	Not involved	9(75%)	3(8.57%)	0.24	
Lymphovascular Emboli	Present	4(33.33%)	30(85.71%)	3.75	0.047
	Absent	8(66.67%)	5(14.29%)	0.21	

DISCUSSION:

The most frequent cancer in women is breast cancer, particularly in developing nations like India. With the advancement of medical science and the introduction of more modern medicines, surgeons are now working towards the complete eradication of the disease. In this environment, there is a growing need for prognostic as well as predictive indicators to track disease progression, response to treatment, and recurrence so that clinicians can intervene at the right moment and with the right alternative therapy.

The clinically significant progression marker D-dimer level suggests a link between haemostasis and tumour progression.[9] Multiple interactions between the tumour and host occur during metastasis. Metastatic cancer cells need to depart from the main tumour, move into the lymphovascular system, and produce an alternate blood supply at their metastatic site in order to survive. Fibrin remodelling is very probably involved in every stage of metastasis and has been shown to be extremely important for the development of new blood vessels.[10]

Numerous research conducted over the past three decades have demonstrated that the fibrinolytic pathway definitely contributes to tumour angiogenesis, and by extension, definitely contributes to carcinogenesis and metastasis. Patients with breast cancer have been reported to have higher levels of plasminogen activator inhibitors, D-dimer, and other markers of the fibrinolytic pathway. The present study supports previous studies that shown upregulated fibrinolytic activity (plasma D-dimer presence) in malignant disease and elevated fibrinolytic activity (raised D-dimer levels) in metastatic disease.[11]

Among the 47 patients, 35(74.47%) had D dimer value more than 0.5 mg/L. In their study, Bhavesh D et al.[12] compared plasma D-Dimer levels in breast cancer, benign breast diseases, and healthy females. There was no increase in D-Dimer levels in benign breast disease patients or healthy females, but there was a significant increase of plasma D-Dimer levels in breast cancer patients, and its value raised more as the stage increased. In a study conducted by Hermansyah D et al.[13] 46.1% of 111 females with confirmed breast cancer exhibited higher D-dimer levels.

Histopathological features such as tumour grade as determined by MBR grading have long been considered to be predictive markers for disease prognosis. There was an increase in D-dimer levels with increasing grade in the current study. Grade I had the lowest mean value, whereas grade III had the highest (p=0.024). Ghadhban BR et al.14 reported a statistically significant correlation between histopathological grade and mean level d-dimer (p value ≤0.01) which was

comparable to the present study.

Clinical stage and clinically visible lymph nodes were thought to be important prognostic factors. A lymphovascular invasion increases the likelihood of discovering both local and distant metastases. A tumour must first penetrate the lymphatic or arterial lumen before being transferred to a new site and establishing viability in the target tissues in order to successfully metastasis. For microvascular trapping necessary for metastasis, fibrin typically develops around circulating cancer cells.[15]

In the present study an increase in D-dimer levels was noted with increase in tumor size ($p<0.001$), presence of lymph node involvement ($p=0.039$), lymphovascular invasion($p=0.047$) and higher stage (<0.001). This was similar to the study done by Ghadhban BR et al.[14] the d-dimer level was high in the breast carcinoma group and high in the group of benign breast tumours (0.25 mg/l). The d-dimer level was rising in the group of advanced breast carcinomas with enlarged tumour size, higher stage and grade, lymphovascular invasion, and lymph node involvement.

Gochhait S et al.[16] observed that D dimer levels were significantly higher in individuals with lymph node involvement, regardless of the number of nodes affected. For a threshold value of 0.765 for D-dimer, the receiver operating characteristic curve provided a sensitivity of 56% and a specificity of 91% for predicting the likelihood of lymph node metastases before surgery. In the study conducted by Sringeri RR et al.[17] D-dimer levels directly linked with the degree of involvement of lymph node and lymphovascular invasion; correlation was found with the positive lymph nodes but not with tumour size.

According to the study conducted by Dai H et al.[18] individuals with breast cancer ($P=0.0022$), gastric cancer (P0.0001), pancreatic cancer ($P=0.0003$), colon ($P=0.0001$), and rectal cancer ($P=0.0028$) had considerably higher plasma levels of D dimer than did healthy controls. Additionally, it was found that there was a positive correlation between plasma D dimer levels and the clinical cancer stage ($P<0.05$) and metastasis ($P<0.05$).

In contrast to the present study, Plasma D dimer was reported to be elevated in advanced clinical stages, higher histologic grades, and the presence of lymphovascular invasion by Amritsar S et al.[19] However, no connection could be observed between D dimer levels and axillary lymph node status. Additionally, Halugodu AS et al.[20] noted that lymph node involvement, lymphovascular invasion, and advanced disease stage all resulted with higher plasma D-dimer levels. There was no statistically significant association between tumour size and histological grade.

CONCLUSION:

The results of the current study clearly demonstrated that individuals with breast cancer had higher plasma D-Dimer levels. D-dimer was a straightforward, non-invasive, rapid, and less expensive laboratory test that may be used as a guide for axillary lymph node dissection after tumour excision in cases of breast cancer and as a predictor of showing lymph node metastases preoperatively. Larger sample size studies are needed to assess the decisive function of various coagulation markers in patients with operable breast cancer for preoperative prediction of lymph node metastases.

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Conflicts Of Interest:
There are no conflicts of interest

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