ORIGINAL RESEARCH PAPER

Volume-7 | Issue-9 | September-2018 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

D-DIMER : A HELPING TOOL IN DETERMINING THE PROGNOSIS IN BREAST CARCINOMA

Surgery

Dr Sumita A Jain	General Surgery, Sawai Man Singh Medical college & Hospital ,India
Dr Atul Ameta*	General Surgery, RNT Medical college, Udaipur in place of Sawai Man Singh Medical college & Hospital, India. *Corresponding Author
Dr Mohit Budhgurjar	General Surgery, Sawai Man Singh Medical college & Hospital ,India
Dr Harish Chand choudhary	General Surgery, Sawai Man Singh Medical college & Hospital ,India
Dr Mohd. Irfan	General Surgery, Sawai Man Singh Medical college & Hospital ,India
Dr Laxman Agarwal	General Surgery, Sawai Man Singh Medical college & Hospital ,India

ABSTRACT

This study was to find out Correlation of Plasma D-Dimer levels in Breast Cancer Patients with Clinical Stage, Lymph Node Metastasis and Hormone receptor status. 36 breast patients of breast neoplasm according to selection criteria were included in this study which after triple assessment were evaluated for D-Dimer status. In this study of 36 patients of breast neoplasm, statistically significant association was found between plasma D-Dimer levels and clinical stage of breast cancer(p value=.0025). Proportion of plasma D-Dimer positive cases with higher stage of tumor was more compared to plasma D-Dimer negative cases.No significant association was observed between plasma D-Dimer levels and mean age of patients, pathology of the tumor Lymph node metastasis, hormone receptor status and Her-2/neu receptor over expression.

KEYWORDS

Breast Cancer, D-Dimer

INTRODUCTION

Breast cancer, the most common female malignancy, represents a heterogeneous group of tumors, which present with both varied behaviors and response to therapy. The development of distant metastases is the primary cause of death in breast cancer patients.[1]

Fibrin deposition and remodeling in the tumor extracellular matrix is an important initial step in tumor metastasis. Activation of intravascular fibrin formation and degradation has been shown to occur in the plasma of breast cancer patients.[5] D-Dimer, a fibrin degradation product, is produced when factor XIIIa, is degraded by plasmin generated from plasminogen by the action of serine protease tissue plasminogen activator.[6]

Hence, D-Dimer levels are elevated in the plasma of various solid tumor patients; including lung, prostate, cervical and colorectal cancer patients.[8]In patients with operable breast cancer, D-Dimer levels have been shown to be elevated at time of diagnosis and to decrease during adjuvant chemotherapy.[9,10]

Cancer is frequently associated with activation of the hemostatic system and the extent of this activation has been reported to correlate with a more advanced tumor stage, with unfavorable outcomes and the patient's prognosis in small studies of patients with breast cancer. D-Dimer is a biomarker that globally indicates the activation of Hemostasis and fibrinolysis[11]

Overall evidences emphasize on the significance of increased plasma D-Dimer levels as a predictor for more rapid tumor growth, presence of more widespread disease and for shorter survival in breast cancer patients.The primary aim of this study is to evaluate the correlation between pre-treatment plasma D-Dimer levels in breast cancer patients with clinical stage, lymph node metastasis and hormone receptor status

AIM

This study was to find out Correlation of Plasma D-Dimer levels in Breast Cancer Patients with Clinical & TNM Stage, Lymph Node Metastasis and Hormone receptor status.

MATERIAL AND METHODS

It is a analytical type of observational study done on all the cases of breast neoplasm (Benign or Malignant) admitted in the Deptt. of Surgery, S.M.S. Medical College & Hospital from February 2013 onward.

SELECTION CRITERIA

All neoplastic breast tumor patients.

While, patients who refused to D-Dimer test, who had undergone excision or incisional biopsy, lumpectomy or mastectomy and who have procured chemotherapy in the past,other concurrent conditions known to increase D-Dimer levels, such as DVT, pregnancy, carcinoma of lung, prostate, cervix and colon, were excluded from the study

METHODOLOGY

After detailed history of the disease course including any previous treatment either operative /chemotherapy, 'Triple assessment' (clinical and radiological examination, FNAC / Trucut biopsy) was done to confirm the diagnosis. D-Dimer assay was done by a semi-quantitative method. Cut off value of plasma D-Dimer is 0.5mcg/ml (fibrinogen equivalent products).

D-Dimer status then correlated with the results and significance of difference in proportion was inferred with Chi square test of significance.

STATISTICAL ANALYSIS:

The qualitative data were presented as proportion and percentage and the quantitative data were presented as mean and standard deviation. 'Student's t test' was used to find out the significance of study parameters on continuous scale and the difference in proportion were analyzed by using chi square test. Significance is assessed at 5% level of significance. P value <0.05 was consider significant.The statistical software SPSS 20 and primer were used for the data analysis and Microsoft word and MS excel have been used to generate graphs and tables.

FIGURES AND TABLES

FIGURE 1.

Association of plasma D-Dimer with mean size of the tumor

D-Dimer	N	Mean size(cm.)	Std. Deviation
Negative	26	4.50	2.214
Positive	10	5.05	1.787
Total	36	4.65	2.094

P value.488 (not significant)

FIGURE 2.
Association of plasma D-Dimer with lymph node status

	D-Dimer Negative		D-Dimer Positive		Total	
Positive lymph nodes	**No**	**%**	**No**	**%**	**No**	**%**
0	11	52.38	3	37.5	14	48.3
2	4	19.05	0	0	4	13.8
3	5	23.81	1	12.5	6	20.7
4	1	4.76	2	25	3	10.3
5	0	0.00	1	12.5	1	3.4
6	0	0.00	1	12.5	1	3.4
Total	**21**	100.00	**8**	100	**29**	100.0

(Chi-square = 9.691 with 5 degrees of freedom; P = 0.090 NS)

FIGURE 3.A
Association Of Clinical Stage Of The Tumor With Plasma D-dimer Levels

	Negative		Positive		Total	
Clinical Stage	**No**	%	**No**	%	**No**	%
IIA	7	30.44	0	0	7	21.88
IIB	11	47.83	2	22.22	13	40.63
IIIA	3	13.04	1	11.11	4	12.50
IIIB	0	0	5	55.56	5	15.62
IV	2	8.69	1	11.11	3	9.37
Total	23	100	9	100	32	100

(Chi-square = 17.336 with 4 degrees of freedom; P = 0.0025)

FIGURE 3.B

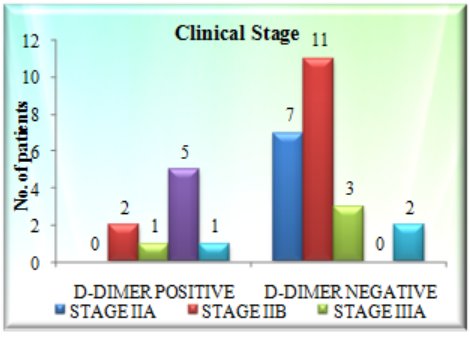
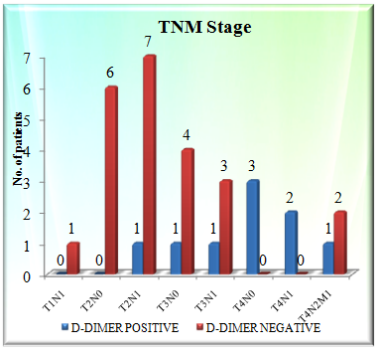


FIGURE 4.A
Association Of TNM Stage Of Tumor With Plasma D-dimer Status

	Negative		Positive		Total	
CLINICAL STAGE	**No**	**%**	**No**	**%**	**No**	**%**
T1N1	1	4.35	0	0	1	3.12
T2N0	6	26.08	0	0	6	18.72
T2N1	7	30.43	1	11.11	8	25
T3N0	4	17.39	1	11.11	5	15.65
T3N1	3	13.05	1	11.11	4	12.50
T4N0	0	0.00	3	33.33	3	9.38
T4N1	0	0.00	2	22.23	2	6.25
T4N2M1	2	8.70	1	11.11	3	9.38
Total	23	100.00	9	100	32	100

FIGURE4.B



OBSERVATION & DISCUSSION

Both experimental and clinical studies have evidenced an association between cancer and Hemostasis. Over the years, investigators have documented the importance of the fibrinolytic pathway in tumor angiogenesis and metastasis.[1-8,29-31] Indicators of fibrinolytic pathway activation, such as levels of plasminogen activator inhibitor and urokinase plasminogen activator, have been shown to have prognostic significance in patients with breast cancer.[5-8]

The prognosis of breast carcinoma is related to a large variety of clinical and pathological factors such as age, histological subtype, tumor size, histological grade, lymph node metastasis and estrogen, progesterone and Her-2/neu receptor status which may help in predicting prognosis and the need for adjuvant therapy.[1,2]

Our study represents an attempt to look at a product of fibrin degradation (D-Dimer) as a specific marker for extent of disease, hormone receptor status and Her-2/neu over expression in human breast cancer.

In our study, Out of 36 patients with breast neoplasm, 19 patients (52.77%) were >45 years of age and 17 patients (47.23%) were < 45 years with a mean age of 42.08 years. The mean age of patients with positive plasma D-Dimer, was more than plasma D-Dimer negative patients. But we could not find statistically significant association between patient age and plasma D-Dimer as we had limited number of patients in the study.

Tumor size is useful predictor of prognosis in breast cancer. Plasma D-Dimer was positive in 10 out of 36 breast tumor patients with a mean tumor size of 5.05cm and negative in 26 patients with mean tumor size of 4.50cm (range= 2 to 12 cm.). In our study, the mean tumor size was higher in patients who were plasma D-Dimer positive but it was not statistically significant [p value=0.488]. Our study was comparable with Dirix LY et al.[19] who also did not find direct correlation between tumor size and D-Dimer levels.(Figure1)

Out of 29 operable/locally advanced breast cancer patients, 100% of patients (n=29) had axillary lymph node dissection. a median of 16 lymphnodes were removed in dissection. and 15 patients (51.73%) had involved lymph nodes ranging from 2 to 6. This shows that we had patients with more aggressive disease as compared to other studies

In our study out of 29 patients who underwent axillary lymph node dissection, 15 patients (51.73%) had involved lymphnodes. 5 (33.33%) out of these 15 lymphnode positive patients were plasma D-Dimer positive. 14 patients (48.27%) had no positive lymph node. 3 out of these 14 lymphnode negative patients (21.42%) were plasma D-Dimer positive. The association of plasma D-Dimer levels and lymph node metastasis was not statistically significant (p value =0.090), which was comparable to other studies done by Fregoni V et al & Batschauer AP et al[23][21].(Figure2)

In this study 66.6% of patients who presented with stage III breast cancer were plasma D-Dimer positive. Only 2 patients with stage II disease (9.52%) were plasma D-Dimer positive. We found statistically significant association between clinical stage of breast cancer patients and their plasma D-Dimer levels. Our study was supported by results of various other studies including study done by Malik Zeb Khan et. al[28]. All of them observed a strong correlation between plasma D-Dimer levels and tumor stage in breast cancer patients (P value=0.001) [11] [19][20]. (Figure3a & 3b)

Out of 32 breast cancer patients, 21.8% of patients (n=7) presented with stage T1N1 and stage T2N0 tumor. 25% of patients had stage T2N1 tumor, 15.62% of patients (n=5) had stage T3N0, and 12.55% of patients (n=4) had stage T3N1 tumor. Stage T4N0 tumor was present in 9.38% (n=3) and 6.25% of patients (n=2) had stage T4N1 disease. 9.38% (n=3) of patients had metastatic breast cancer (T4N2M1).. As compared to study done by Malik Zeb Khan et. al, patients presenting with earlier TNM stage were more in our study.[28]

Significant association(p value=0.023) was observed in plasma D-Dimer and TNM stage of the tumor**.** Proportion of the cases with positive D-Dimer status were more in T4N0 and T3 N1 stage as compared to T2 N0 and T2 N1 stage of the tumor.(Figure 4a & 4b)

The overall tumor load measured by TNM staging of the carcinoma breast was associated with significant elevation of the plasma D-Dimer levels (p value=0.023). In various studies [19][20][22] they also observed

significant association of tumor load and plasma D-Dimer in breast cancer patients (p value<0.01).

No significant association was observed between plasma D-Dimer and hormone receptor status in breast cancer patients and the result was consistent with the studies done by others[19][25] (p value > 0.34).

CONCLUSION

Estimation of the prognosis in a breast cancer patient is of utmost clinical interest and helps when making decisions on the type and intensity of treatment. Plasma D-Dimer, as a marker of activation of hemostatic system, reflects the ongoing metastasis and extent of disease and thus helps in determining the prognosis.

In this study, we observed significant association of plasma D-Dimer levels with stage of the breast cancer. Patients with higher stage of tumor had elevated levels of D-Dimer in their plasma compared to patients with lower stage tumor and consequently bad prognosis. Higher proportion of patients with increased tumor burden measured by TNM staging were associated with raised plasma D-Dimer. But, it does not have any significant correlation with age, pathology, receptor status, lymph node metastasis and Her-2/neu over expression.

Plasma D-Dimer level positively correlates with clinical stage of breast cancer. Higher D–Dimer levels predict aggressiveness of the tumor. So it can be a prognostic marker of poor outcome in patients with breast cancer. A patient with operable breast cancer and elevated D-Dimer levels is almost three times more likely to have agressive disease as compared with the patient with low plasma D-Dimer. This suggests that a patient with small tumor and low plasma D-Dimer levels could possibly be spared of the morbidity of axillary lymphnode dissection.

An important role of D-Dimer could be in combination with other predictive factors in determining whether or not axillary lymphnode dissection is necessary. As this study clearly supports a role of plasma D-Dimer in predicting aggressiveness of the disease, it should be investigated as a prognostic marker of operable breast cancer and the usefulness of combining plasma D-Dimer with sentinel lymphnode biopsy to avoid complete Axillary lymphnode dissection has to be evaluated.

Measurement of plasma D-Dimer is not time consuming, require only a small plasma aliquot and is cost effective. Therefore plasma D-DIMER should be evaluated in all patients with newly diagnosed breast cancer.

REFERENCES

1. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer 1989;63:181-187.
2. Rock CL, Flatt SW, Laughlin GA, et al. Reproductive steroid hormones and recurrence-free survival in women with a history of breast cancer. Cancer Epidemiol Biomarkers Prev 2008;17:614-620.
3. Edwards RL, Rickles FR, Moritz TE, Henderson WG, Zacharski LR, Forman WB, et al. Abnormalities of blood coagulation tests in patients with cancer. Am J Clin Pathol. 1987;88(5):596–602. [PubMed]
4. Fidler IJ, Ellis LM: The implications of angiogenesis for the biology and therapy of cancer metastasis. Cell 79:315-328, 1994
5. Grohndahl-Hansen J, Agerlin N, Munkholm-Larsen P: Sensitive and specific enzyme-linked immunosorbent assay of urokinase-type plasminogen activator and its application in plasma from patients with breast cancer. J Lab Clin Med 111:42-51, 1988
6. Wilde JT, Kitchen S, Kinsey S, et al: Plasma D-Dimer levels and their relationship to serum fibrinogen/fibrin degradation products in hypercoaguable states. Br J Haematol 71:65-70, 1989
7. Bick RL, Baker WF: Diagnostic efficacy of the D-Dimer assay in disseminated intravascular coagulation (DIC). Thromb Res 65:785-790, 1992
8. D-Dimer and prothrombin fragment 1+2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. Ay C, Vormittag R, Dunkler D, Simanek R, Chiriac AL, Drach J, Quehenberger P, Wagner O, Zielinski C, Pabinger I J Clin Oncol. 2009 Sep 1; 27(25):4124-9.
9. McCollough P, Douglas J, Lowe GDO, et al: In vivo measurement of fibrin formation and fibrinolysis in operable breast cancer. Thromb Haemost 61:318-321, 1989
10. Tempelhoff GF, Dietrich M, Hommel G, et al: Blood coagulation during adjuvant epirubicin/cyclophosphamide chemotherapy in patients with primary operable breast cancer. J Clin Oncol 14:2560-2568, 1996
11. Blackwell K, Haroon Z, Broadwater G, Berry D, Harris L, Iglehart JD, et al. Plasma D-Dimer levels in operable breast cancer patients correlate with clinical stage and axillary lymph node status. J Clin Oncol. 2000;18(3):600–8. [PubMed]
12. Dirix LY, Salgado R, Weytjens R, Colpaert C, Benoy I, Huget P, van Dam P, Prové A, Lemmens J, Vermeulen P. "Plasma fibrin D-Dimer levels correlate with tumour volume, progression rate and survival in patients with metastatic breast cancer." Br J Cancer. 2002 Feb 1;86(3):389-95.
13. Comparison of plasma D-Dimer and thrombus precursor protein in patients with operable breast cancer as a potential predictor of lymph node metastasis. Kim, Hyun Kyunga; Song, Kyung Soonb; Lee, Kyoung Rhana; Kang, Yoon Heec; Lee, Young-Joonc; Lee, Eun-Sookd Blood Coagulation & Fibrinolysis: January 2004 - Volume 15 - Issue 1 - pp 9-13.
14. D-Dimer as a possible prognostic marker of operable hormone receptor-negative breast cancer. Batschauer AP1, Figueiredo CP, Bueno EC, Ribeiro MA, Dusse LM, Fernandes AP, Gomes KB, Carvalho MG. Ann Oncol. 2010 Jun;21(6):1267-72. doi: 10.1093/annonc/mdp474. Epub 2009 Oct 30.
15. Correlation of D dimer and factor VIII levels with histopathology in patients with breast carcinoma. Khangarot SS1, Gupta N, Goswami B, Hadke NS, Lal P, Gupta N, Khurana N. Cancer Biomark. 2010;7 (6):305-14. doi: 10.3233/CBM-2010-0196.
16. No correlation between plasma D-Dimer levels and lymph node involvement in operable breast cancer. Fregoni V, Regolo L, Da Prada GA, Zambelli A, Baiardi P, Zanini V, Villani L, Pavesi L, Riccardi A. Breast. 2012 Apr;21(2):220. doi: 10.1016/j.breast.2011.11.010.
17. Coagulation assays in breast cancer: Correlation of plasma D-Dimer with tumor load and invasiveness in breast cancer patients. Senem Karabulut, Leyla Kilic, Rumeysa Ciftci, J Clin Oncol 31, 2013 (suppl; abstr e11592)
18. Malik Zeb Khan et. al. Fibrinogen Degradation Products and D-DIMERS in patients with breast carcinoma. Gomal Journal of Medical Sciences Jan–June, 2007, Vol. 5, No. 1
19. Dvorak HF: Tumors: Wounds that do not heal. N Engl J Med 315:1650-1659, 1986
20. Blood CA, Zetter BR: Tumor interactions with the vasculature: Angiogenesis and tumor metastasis. Biochim Biophys Acta 1032:89-118, 1990
21. Ausprunk DH, Folkman J: Migration and proliferation of endothelial cells in preformed and newly formed blood vessels during tumor angiogenesis. Microvasc Res 14:53-65, 1977.