Original Research Article

D-dimer as a safe, convenient and easily available biomarker, when combined with conventional sentinel node biopsy in clinically node negative breast cancer to assess metastatic disease in axilla and reduce false negative results

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ABSTRACT

Background: Breast cancer is frequently associated with activation of the hemostatic system and the extent of this activation correlates with a more advanced tumor stage. D-dimer is a biomarker that indicates the activation of hemostasis and fibrinolysis.

Methods: This is a prospective, observational, analytical study in which we compare plasma D-dimer levels among three groups i.e., healthy subjects, benign patients and breast cancer patients. We have also evaluated plasma D-dimer levels in patients with lymphadenopathy and in those patients who did not have palpable lymph nodes. Plasma D-dimer levels were further characterized based on TNM classification in breast cancer patients where quantitative D-dimer levels were correlated with clinical stage grouping.

Results: Through our study we have observed that D-dimer level is inexpensive and a convenient method for diagnosis and prognosis of breast cancer. We have used a control group so as to evaluate a more accurate result. Comparison between benign and malignant lesions was made and we have achieved a significant p value, which proved our study positive for raised D-dimer levels in cancer breast.

Conclusions: D-dimer proves to be a safe, convenient and easily available biomarker which can be combined with conventional sentinel node biopsy in clinically node negative breast cancer to assess metastatic disease in axilla and reduce false negative results. Plasma D-dimer level was positively correlated with clinical stage of solid cancers.

Keywords: D-dimer, Breast cancer, Biomarkers, Diagnostic marker, Randomized control trial, Metastasis

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer and the leading cause of death in women world-wide. It accounts for about 23% of the total cancer cases and 14% of the total cancer-related deaths. Globally, breast cancer now represents one in four of all cancers in women. However, 60% of the breast cancer-related deaths have been found to occur in economically developing countries such as India.

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. D-dimer is a biomarker that globally indicates the activation of hemostasis and fibrinolysis. It is a degradation product of fibrin, which is produced when cross-linked fibrin is degraded by plasmin-induced fibrinolytic activity. Elevated D-dimer levels may also be observed in other clinical settings such as cancer,
pregnancy and infectious diseases or following trauma and surgery.

For daily practice, D-dimer may be a suitable test for evaluation of disease extent before designing treatment strategy. Assays of D-dimer may serve as the useful strategy for disease monitoring in patients undergoing therapy.

The current study compares plasma D-dimer levels among three groups’ i.e., healthy subjects, benign patients and breast cancer patients. We have also evaluated plasma D-dimer levels in patients with lymphadenopathy and in those patients who did not have palpable lymph nodes. Plasma D-dimer levels were further characterized based on TNM classification in breast cancer patients where quantitative D-dimer levels were correlated with clinical stage grouping.

**Aim and objectives**

Aim of the study was to evaluate the reciprocal relation of the quantitative plasma D-dimer levels as the biomarker for early tumor metastasis in the operable breast lumps.

Objectives of the study were to evaluate plasma D-dimer levels in benign breast lumps, to evaluate plasma D-dimer levels in malignant breast lumps, to evaluate plasma D-dimer levels in healthy individuals and to obtain the reciprocal relation of quantitative plasma D-dimer levels as a marker for early tumor metastasis in operable breast lumps.

**METHODS**

**Enrolment of patients**

All patients with breast lump admitted in Bharati hospital and research centre, Pune. The review board of our institute for ethical research approved the study protocol. The study was carried out between August 2013 to August 2015.

**Patient randomization**

This was a prospective, observational, analytical study in which we studied patients in three different groups. The patients were randomly assigned to three different groups: group A (Control): 21 patients with no known history of any illness, group B (Benign): 37 patients having breast lump and group C (Malignancy): 44 confirmed breast cancer patients.

**Study type**

The study was of prospective, observational, analytical study.

**Inclusion criteria**

All adult patients suffering from any breast lump and was operable were included in the study.

**Exclusion criteria**

Patients who had breast abscess, thromboembolic disease, disseminated intravascular coagulation, liver disease, any other malignancy, trauma, high rheumatoid factor, pregnancy and male breast cancer were excluded from the study.

**Methodology used**

All cases of breast lumps coming to surgery O. P. D. or getting admitted in surgery ward of Bharati hospital and research centre were included in the study. Detailed case history of the patient was recorded as in the proforma. Detailed clinical examination of the patient was performed as in the proforma. Necessary investigations were carried out as in the proforma. A Plasma D dimer level was sent prior to operating. Plasma D dimer levels were further correlated with the histopathological findings and patients’ data was subjected to statistical analysis to find out statistically significant levels.

**Statistical methods**

**Frequencies distribution**

It summarizes the distribution of values in the sample. Distribution of values could be done according to age, sex or by other means and a table could be created to display the frequency of various outcomes in our studied groups.

**T test**

A t-test compares the means of two groups. The t test compares one variable (e.g., D-dimer level) between two groups. The t tests (and related nonparametric tests) compare exactly two groups.

**Tukey's multiple comparison test**

Tukey’s multiple comparison test can be used to determine which means amongst a set of means differ from the rest. When we have >2 groups, it is inappropriate to simply compare each pair using a t test because of the problem of multiple testing. The correct way to do the analysis is to use a one-way analysis of variance (ANOVA) to evaluate whether there is any evidence that the means of the populations differ. If means of the populations differ, we might then be interested in investigating which of the means are different. This is where the Tukey’s multiple comparison test is used. The Tukey’s test compares every mean with every other mean.
Software used

All the statistical calculations were done through Graph pad Prism software for windows.

RESULTS

Patients’ distribution

In this study, total 102 subjects were randomized in three different groups. Control group (Group A) included 21 healthy subject and no known history of any past illness. Benign group (Group B) had 37 fibroadenoma patients. Malignancy (Group C) had 44 patients who were diagnosed for breast cancer. Diagnosis of benign and malignancy was confirmed by mammography and then FNAC report.

Age group

Most of the patients presenting with breast diseases were in the 4th decade of life in both the groups. Health control group had 9 patients (42.86%) and benign group had 12 patients (32.43) in 4th decade. Malignancy group had 18 patients (40.91%) in 4th decade and 19 patients (43.18%) in 5th decade (Figure 1).

![Figure 1: Age wise distribution of health control, benign and malignant patients.](image)

 Plasma D-dimer levels in healthy subjects

We have studied a control group, to establish normal level of plasma d-dimer in our study population. We reported 168.7±46.77 ng/ml d-dimer in control subject. Here, the minimum D-dimer values was 102.0 ng/ml and the upper value was 296 ng/ml.

 Plasma D-dimer levels in benign patients

We have studied a group of benign patients, most of which were fibroadenoma cases. We reported 197.2±72.66 ng/ml d-dimer in benign patients. Here the minimum D-dimer value was 53.40 ng/ml and the upper value was very high i.e., 423 ng/ml.

 Plasma D-dimer levels in breast cancer patients

We have studied a group of cancer breast patients, to establish a level of plasma d-dimer in cancer patients. We reported 417.2±176.8 ng/ml d-dimer in cancer patients. Here, the minimum D-dimer values was 92.40 ng/ml and the upper value was very high i.e., 977 ng/ml.

Comparative plasma D-dimer levels in studied groups

We compared three groups for plasma d-dimer level. The median plasma D-dimer level was significantly higher in patients with breast carcinoma than those patients with benign breast diseases and healthy subjects. However, we did not find a significant difference between control and benign patients (p=0.69). We also reported a significant difference between benign and malignant group (p=0.0001) as malignant group showed very high values compared to benign group (197.2 versus 417.2 ng/ml) (Figure 2).

![Figure 2: The box-and-whiskers plots extended from the 25th to 75th percentiles. The line in the middle of the box was plotted at the median. The whiskers go down to the smallest value and up to the largest.](image)

 Plasma D-dimer levels in patients with lymphadenopathy

We analyzed d-dimer level in lymphadenopathy positive and negative patients. There were 21 and 23 breast cancer patients who were positive and negative for the lymphadenopathy, respectively. Here, we reported a significant higher plasma d-dimer value in lymphadenopathy patients compared to those patients who were negative for lymphadenopathy (p<0.0001) (Figure 3).
Figure 3: Plasma D-dimer levels in lymphadenopathy.

We have analyzed our data for tumor size and related D-dimer level in the studied patients. We reported more number of patients in T4 category and lesser number of patients in T1 category. Small tumor size T1 showed very low level of plasma D-dimer level compared to T2-T4. Patients having T4 tumor stage showed significantly very high level of plasma D-dimer level compared to other tumor grade (Table 1 and 2).

Table 1: Plasma D-dimer level in relation to tumor size.

| Variables          | N0   | N1   | N2   | N3   |
|--------------------|------|------|------|------|
| Number of patients | 6    | 11   | 13   | 14   |
| % of patients      | 13.63| 25   | 29.54| 31.81|
| Minimum (ng/ml)    | 92.40| 190.0| 247.0| 331  |
| Maximum (ng/ml)    | 213.0| 661.0| 762.0| 977  |
| Mean (ng/ml)       | 157.4| 371.0| 448.3| 535.9|
| Std. deviation     | 48.74| 125.2| 144.9| 148  |

Table 2: Tukey's multiple comparisons test.

| Tumor size vs.     | Significant | Summary | P value |
|--------------------|-------------|---------|---------|
| T1 vs. T2          | Yes         |         | 0.0149  |
| T1 vs. T3          | Yes         | ***     | 0.0004  |
| T1 vs. T4          | Yes         | ****    | <0.0001 |
| T2 vs. T3          | No          | NS      | 0.4942  |
| T2 vs. T4          | Yes         |         | 0.0187  |
| T3 vs. T4          | No          | NS      | 0.3307  |

Plasma D-dimer level in relation to lymph nodes

We have analyzed our data for the lymph nodes and related D-dimer level in the studied patients. N0 indicates tumor cells absent from regional lymph nodes, N1 indicates regional lymph node metastasis present, N2 indicates tumor spread to an extent between N1 and N3 and N3 shows tumor spread to more distant or numerous regional lymph nodes. We reported more number of patients in N1 category and lesser number of patients in N2 category. N3 showed very high level of plasma D-dimer level compared to other N0-N2. Patients having N3 tumor stage showed significantly very high level of plasma D-dimer level compared to other tumor grades. (Table 3 and 4).

Table 3: Plasma D-dimer level in relation to lymph nodes.

| Regional lymph nodes | N0 | N1 | N2 | N3 |
|----------------------|----|----|----|----|
| Number of patients   | 11 | 14 | 8  | 11 |
| % of patients        | 25 | 31.81| 18.18| 25 |
| Minimum (ng/ml)      | 92.40| 190 | 322 | 531 |
| Maximum (ng/ml)      | 370 | 499 | 574 | 977 |
| Mean                 | 234.9| 366.1| 465.3| 629.6|
| Std. deviation       | 97.30| 366.1| 74.68| 133.5|

Table 4: Tukey's multiple comparisons test.

| Regional lymph nodes | Significant | Summary | P value |
|----------------------|-------------|---------|---------|
| N0 vs. N1            | Yes         | *       | 0.0371  |
| N0 vs. N2            | Yes         | ***     | 0.0004  |
| N0 vs. N3            | Yes         | ****    | <0.0001 |
| N1 vs. N2            | No          | NS      | 0.1474  |
| N1 vs. N3            | Yes         | ****    | <0.0001 |
| N2 vs. N3            | Yes         | **      | 0.0072  |

Plasma D-dimer level in relation to metastasis

We have analyzed our data for the metastasis and related D-dimer level in the studied patients. MX indicates distant spread (metastasis) cannot be assessed, M0 indicates no distant metastasis and M1 shows metastasis to distant organs (beyond regional lymph nodes). We reported more number of patients in M0 category and lesser number of patients in MX category. MX and M0 did not showed any significant difference in plasma d-dimer level (p=0.9452). Patients having M1 tumor stage showed significantly very high level of plasma D-dimer level compared to other tumor grade (Table 5 and 6).

Table 5: Plasma D-dimer level in relation to metastasis.

| Metastasis | MX | M0 | M1 |
|------------|----|----|----|
| Number of patients | 7  | 21 | 16 |
| % of patients     | 15.90| 47.72| 36.36|
| Minimum (ng/ml)   | 190 | 92.40| 495.3|
| Maximum (ng/ml)   | 447 | 471 | 977 |
| Mean              | 327.5| 311.4| 595.3|
| Std. deviation    | 85.67| 117.6| 122.2|
Table 6: Tukey’s multiple comparisons test.

| Metastasis  | Significant | Summary | P value  |
|-------------|-------------|---------|----------|
| MX vs. M0   | No          | NS      | 0.9452   |
| MX vs. M1   | Yes         | ****    | <0.0001  |
| M0 vs. M1   | Yes         | ****    | <0.0001  |

**DISCUSSION**

D-dimer is a stable end product of fibrin degradation. Activation of coagulation and fibrinolysis is frequently associated with malignancy. Half of all cancer patients and approximately 90% of cancer patients with metastatic disease have abnormal coagulation parameters, which might be a sign of subclinical activation of the coagulation and fibrinolytic systems.1 The extent of activation of coagulation and fibrinolysis has been reported to correlate with tumor stage and prognosis in some malignancies, such as non-small-cell lung cancer, colorectal, and breast cancer.2-4 Here, we studied D-dimer levels of 81 patients with benign and malignant breast diseases and compared our data with healthy controls.

**Plasma D-dimer levels in healthy subjects and benign breast disease patients**

We reported mean values of 168.7±46.77 ng/ml d-dimer in healthy control subject. On the other hand, benign patients showed 197.2±72.66 ng/ml d-dimer level. Benign patients showed little higher values for d-dimer compared to health subjects. However, unpaired t test resulted into non-significant difference between healthy subjects and benign breast lesion patients (p=0.1122).

Our results are not in agreement to Tempelhoff et al.3 He reported that healthy subjects have significantly lower D-dimer level (290±200 ng/ml; normal range: 20-400 ng/ml; n=125) compared to benign breast patients (422±425 ng/ml; n=164). The reason for this difference might be due to sample size as Tempelhoff et al included 125 health controls and 164 Patients with benign tumors.5

**Plasma D-dimer levels in healthy subjects and breast cancer patients**

We compared three groups for plasma d-dimer levels. The median plasma D-dimer level was significantly higher in breast carcinoma patients than the healthy control. We also reported significant difference between healthy control and malignant group (p=0.0001) as malignant group showed very high values compared to healthy group.

Similarly, Mitter and Zielinski reported significantly elevated plasma d-dimer level in 73 female breast cancer patients, as compared to healthy controls (p<0.0001). In addition, they also observed a moderate correlation between d-dimer and other biomarker such as CA15-3 (r=0.40; p<0.001) and carcinoembryonic antigen (r=0.39; p<0.01).6

Falanga et al studied 32 breast cancer patients and compared to those of a sex and age-matched non-cancer control group. There were significant elevation of plasma levels of D-dimer (p<0.0001) compared to controls.7

Batschauer et al studied 32 patients with operable hormone receptor-negative breast cancer and a control group with 43 healthy women. Plasma D-dimer level was normal in the control group and significantly higher in breast cancer patients (p<0.0001).8

Tempelhoff et al studied 50 consecutive node-positive breast cancer patients for D-dimer.9 Preoperative levels of D-dimer level were significantly higher than in healthy women. Tempelhoff et al reported that healthy patients have lower D-dimer level (290±200 ng/ml; normal range: 20-400 ng/ml) compared to breast cancer patients (581±634 ng/ml).3

**Plasma D-dimer levels in benign and malignant mammary diseases**

The median plasma D-dimer level was significantly higher in patients with breast carcinoma than those patients with benign breast disease. We also reported significant difference between benign and malignant group (p=0.0001) as malignant group showed very high values of d-dimer level compare to benign group.

Similarly, Neises et al demonstrated significantly increased d-dimers in 128 female mammary carcinoma patients compared to the control group having benign mammary disease (p<0.01).10 He also noted that sensitivity and specificity of d-dimer were slightly higher than those of the established tumour marker CA 15-3 and CEA. Based on his study, he suggested possible use of plasma d-dimer as tumour markers. Blackwell et al reported significantly higher median plasma D-dimer levels in invasive carcinoma patients than those patients with either benign breast disease or carcinoma-in-situ (p=0.0001).11 Tempelhoff et al reported that benign patients has lower D-dimer level (422±425 ng/ml; normal range: 20-400 ng/ml) compared to breast cancer patients (581±634 ng/ml).5

**Plasma D-dimer levels in patients with lymphadenopathy**

There were 21 and 23 breast cancer patients who were positive and negative for the lymphadenopathy, respectively. Here, we reported a significant higher plasma d-dimer value in lymphadenopathy patients compared to those patients who were negative for lymphadenopathy (p<0.0001) (Table 7).

Batschauer et al studied 32 patients with operable hormone receptor-negative breast cancer.8 The results...
showed that plasma D-dimer levels were not correlated with clinical and histopathology findings (p=0.213). The results taken together indicate the presence of a hypercoagulability state in women with operable hormone receptor-negative breast cancer given the increased levels of D-dimer in this group. Therefore, considering higher levels of D-dimer in patients with a poor outcome, its evaluation may be a promising tool for prognosis in women with operable hormone receptor-negative breast cancer.

**Table 7: Plasma D-dimer levels in patients with lymphadenopathy.**

| Variables   | Negative | Positive |
|-------------|----------|----------|
| Number of patients | 21        | 23        |
| Minimum (ng/ml)     | 92.40    | 387.0    |
| Maximum (ng/ml)     | 442.0    | 977.0    |
| Mean (ng/ml)        | 276.4    | 545.8    |
| Std. deviation      | 96.97    | 127.7    |

Blackwell et al studied 140 preoperative plasma specimens obtained from women scheduled to undergo diagnostic breast biopsies.\(^{11}\) Median plasma D-dimer levels were significantly higher in patients with invasive carcinoma than those patients with either benign breast disease or carcinoma-in-situ (p=0.0001). A significant relationship existed between the presence of elevated D-dimer (>100 ng/mL) and involved axillary lymph nodes (p=0.001). Quantitative D-dimer levels were highly correlated with clinical stage grouping (p=0.002). This correlation suggests that detectable fibrin degradation, as measured by plasma D-dimer, is a clinically important marker for lympho-vascular invasion and early tumor metastasis in operable breast cancer.

Kim et al studied 98 breast cancer patients and showed that no. of lymph node metastases was positively correlated with D-dimer level (Pearson's correlation coefficient=0.25, p=0.028).\(^{12}\) Dirix et al studied 3 cohorts: group A (n=30) consisted of 30 healthy female volunteers, group B (n=23) of consecutive patients with operable breast cancer and group C (n=84) of patients with untreated/progressive metastatic breast cancer.\(^{13}\) D-dimers were increased in nearly 89% of patients with progressive metastatic disease. Level of D-dimers was positively correlated with tumor load (p<0.0001) and number of metastatic sites (p=0.002). D-dimer level is clinically imp. marker for progression and points towards relation between hemostasis and tumor progression.

Khangarot et al an Indian study, showed significantly higher levels of D-dimer in tumors with significant lympho-vascular and adipose tissue invasion in comparison to localized tumors.\(^{14}\)

**TNM staging and plasma D-dimer level**

We observed that plasma D-dimer levels were higher in breast cancer patients with tumors that were relatively large, more depth of invasion, lymph node metastasis and were at a relatively advanced TNM stage. Those patients who had small tumor and no lymph node involvement and metastasis showed lower level of plasma d-dimer.

We analyzed d-dimer level in the lymphadenopathy positive and negative patients. There were 21 and 23 breast cancer patients who were positive and negative for the lymphadenopathy, respectively. Here, we reported a significant higher plasma d-dimer value in lymphadenopathy patients compared to those patients who were negative for lymphadenopathy (p<0.0001).

**Plasma D-dimer level in relation to tumor size**

We have analyzed our data for tumor size and related D-dimer level in the studied patients. We reported more number of patients in T4 category and lesser number of patients in T1 category. Small tumor size T1 showed very low level of plasma D-dimer level compared to T2-T4. Patients having T4 tumor stage showed significantly very high level of plasma D-dimer level compared to other tumor grade.

Likewise, other cancer studies have also reported as we have reported for TNM staging and plasma D-dimer level. Plasma D-dimer levels were higher in colorectal cancer patients with tumors that were relatively large, had relatively deep wall penetration and were of a relatively advanced TNM stage.\(^{14}\) Recently, Liu et al demonstrated that elevated plasma D-dimer was correlated with depth of invasion, lymph node metastasis, peritoneal dissemination, distant metastasis, tumour size, TNM stage, and worse overall survival in gastric cancer.\(^{15}\) The relationship between preoperative plasma D-dimer level and both pathological findings and TNM classification and the prognostic significance of preoperative plasma D-dimer level was examined by Oya et al in 93 patients who underwent curative resection of colorectal cancer.\(^{3}\) There were seven cases in stage 0, 10 cases in stage I, 30 in stage II and 36 in stage III. They found that plasma D-dimer levels were significantly higher in patients with moderately differentiated adenocarcinoma, larger tumors, deep-wall penetration and advanced TNM stages.

The preoperative plasma D-dimer level correlated with pathological findings of the tumors and TNM stage.\(^{14}\) Blackwell et al showed significant relationship between the presence of elevated D-dimer (>100 ng/mL) and involved axillary lymph nodes in breast cancer patients. D-dimer levels correlated with clinical stage, lympho-vascular invasion and axillary lymph node involvement in operable breast cancer and D-dimer was suggested to be a biomarker for predicting early tumor metastases.\(^{11}\)

Through our study we have observed that D-dimer level is inexpensive and a convenient method for diagnosis and prognosis of breast cancer. We have used a control group so as to evaluate a more accurate result. Comparison
between benign and malignant lesions was made and we have achieved a significant p value, which proved our study positive for raised D-dimer levels in carcinoma Breast.

Limitations

Limitations of this study include its limited sample size, financial implication on a patient of lower economic strata for determining D-dimer levels, lack of facilities (especially in a rural setup) capable of determining plasma D-dimer levels, and a further study is needed to determine the value and proper usage of D-dimer levels in the diagnosis, prognosis, and follow-up of breast malignancies.

CONCLUSION

This study proves that D-dimer levels may be a safe, convenient, reliable and an easily available biomarker which when combined with conventional sentinel node biopsy in clinically node negative breast cancers to assess metastatic disease in axilla and reduces false negative results. This study also proves that plasma D-dimer levels might be useful in patients with breast tumors as a diagnostic marker. Plasma D dimer levels also positively correlates with clinical stage of solid cancers. While elevated plasma D dimer could be a novel biomarker for advanced stage of a patient with solid cancer.

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