Original Research Article

Correlation of plasma D-dimer levels with breast carcinoma

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ABSTRACT

Background: Breast cancer is the most commonly occurring cancer in women. There is a correlation between cancer and hyper coagulation. Carcinoma increases the level of cross-linked fibrin degradation product (plasma D-dimer), indicative of systemic activation of fibrinolysis, hemostasis and angiogenesis. This study attempted to correlate raised plasma D-dimer in breast cancer.
Methods: A retrospective study was conducted in the department of general surgery in GCS hospital, Ahmedabad where in patients admitted and treated for breast cancer between July 2020 to June 2021 were selected. Plasma D-dimer levels were correlated with final histopathological examination of breast specimen.
Results: Plasma D-dimer levels were increased with advancing stage of disease, lymph node involvement and lymphovascular invasion. There was no significant relationship with increase in tumour size and histopathological grade of tumour.
Conclusions: Plasma D-dimer levels are elevated in breast cancer, especially with advanced stage. It is an important marker of clinical stage, lymphovascular invasion, lymph node involvement. However it does not correlate with tumour size and histological grade. So pre-operative plasma D-dimer level is a safe, cost effective and convenient method for prediction of advanced stage in breast cancer.

Keywords: Breast carcinoma, D-dimer, Advanced stage, Lymphovascular invasion

INTRODUCTION

The most commonly diagnosed cancer is breast cancer with an estimated 2.3 million new cases (11.7%) per year.[2]

In 1865, Trousseau reported a high incidence of venous thrombosis in patients of gastric carcinoma. This established the relationship between neoplastic diseases and thromboembolic disorders.[3]

Hypercoagulability in body is due to complex interaction between cancer cells and host cells causing an impairment in host defense mechanism thus leading to thrombogenesis.[4] Acquired thrombophilia is seen in cancer due to local and systemic effects of cancer as well as the complications of its treatment.[4] Neoplastic cells directly activate blood clotting cascade and cause thrombosis by inducing procoagulant properties and inhibiting anticoagulant properties in the body.[4]

Degradation of cross linked fibrin causes an elevation in plasma D-dimer levels which is indicative of activation of fibrinolysis and hemostasis.[5] Elevated plasma D-dimer is linked to locally advanced breast cancer, metastasis to axillary lymph nodes or distant metastasis.[6]

A tumour metastasizes either through vascular or lymphatic system. Cross linked fibrin is deposited to act as stable framework for progression, migration and invasion.[7]

This study attempted to correlate pre-operative plasma D-dimer levels in patients of breast carcinoma with histopathological parameter and assess its prognostic value.

METHODS

A retrospective study was conducted between July 2020 to June 2021 where female patients admitted and operated for breast cancer at GCS hospital, Ahmedabad were noted by simple random sampling and those fitting the inclusion criteria were selected. Ethical approval was taken from the institutional ethics committee prior to commencement of the study.

Inclusion criteria

Consenting patients with triple assessment proven breast cancer who were operated and their complete histopathological report was available were included in the study.

Exclusion criteria

All patients whose data was incomplete, had history of other forms of cancer, history of previous chemotherapy or radiotherapy, recent history or presence of infection, pregnant women, smokers, on oral contraceptive pills, coagulation disorders, history or presence of thromboembolic events were excluded.

Their preoperative D-dimer levels were collected. In our institute, plasma D-dimer levels were measured using Sysmex CA-50 machine which had a normal range of value of <0.2 mg/l or <200 ng/ml.

Preoperative plasma D-dimer levels were correlated with the following histopathological parameters: tumour size; histological grade (Scarff Bloom-Richardson grade); axillary lymph node involvement; and presence of lymphovascular invasion.

Data was collected and compiled in Microsoft excel. Z test and ANOVA test was applied in SPSS version 24 and p values were calculated.

RESULTS

Total of 35 patients were selected in the study. The age of patients ranged from 37-63 years with mean age of 51.9.

D-dimer level mean was 0.1 in breast cancer stage I. In stage II (both IIA and II B), all patients had D-dimer levels ranging from <0.2-0.5, with a mean of 0.2. In stage III A the mean D-dimer was 0.4 while it was 0.3 in stage III B. 8.57% patients belonged to stage III C and stage IV each, having D-dimer average of 0.5 mg/l and 1.0 mg/l respectively. Thus D-dimer increased with stage advancement. Further, the increase was found to be statistically significant, p=0.0000 (Table 1).

Table 1: Plasma D-dimer levels as per different stages in breast carcinoma.

TNM stage	Number of patients N (%)	Mean D-dimer (mg/l)
Stage I	2 (5.71)	0.1
Stage II A	6 (17.16)	0.2
Stage II B	9 (25.71)	0.2
Stage III A	10 (28.57)	0.4
Stage III B	2 (5.71)	0.3
Stage III C	3 (8.57)	0.5
Stage IV	3 (8.57)	1.0
P value	0.0000 (significant)	

Table 2: Tumour size distribution according to the D-dimer levels.

Tumour size	Number of patients N (%)	Mean D-dimer (mg/l)
T1 (<2 cm)	6 (17.14)	0.2
T2 (2-4.9 cm)	22 (62.86)	0.3
T3 (5 and more)	3 (8.57)	0.5
T4 (any size involving beyond breast tissue)	4 (11.43)	0.6
P value	0.083 (not significant)	

Table 3: Histopathological grade distribution in comparison to D-dimer levels.

Histological grade	Number of patients N (%)	Mean D-dimer (mg/l)
I	4 (11.83)	0.2
II	17 (48.17)	0.3
III	14 (40)	0.4
P value	0.347 (not significant)	

Table 4: Lymph node involvement and plasma D-dimer levels.

Lymph nodes involved	Number of patients N (%)	Mean D-dimer(mg/l)
Involved	28 (80)	0.6
Not involved	7 (20)	0.2
P value	0.008 (significant)	

Table 5: Lymphovascular invasion and D dimer level correlation.

Lymphovascular invasion	Number of patients N (%)	Mean D-dimer (mg/l)
Absent	5 (14.29)	0.1
Present	30 (85.71)	0.5
P value	0.004 (significant)	

Further on comparing plasma D-dimer levels with tumour size, T1 had the least mean, that is, 0.2 mg/l while T4 tumours exhibited a mean of 0.6 mg/l. We saw an increase in D-dimer levels with increase in tumour size. This increase was, however, statistically not significant (p=0.083) (Table 2).

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 of 0.2 mg/l while grade III showed maximum value (Table 3). However, this increase was not statistically significant.

Histopathological report revealed 28 out of 35 patients showed involvement of axillary lymph nodes with an elevated D-dimer level of 0.6 mg/l (Table 4). The rise in plasma D-dimer was statistically significant with p value of 0.008.

On histopathological examination, 85.71% patients with lymphovascular invasion presented with a mean plasma D-dimer of 0.5 mg/l which was higher than the patients without lymphovascular invasion (Table 5) and this result was statistically significant (p=0.004) (Table 5).

The average plasma D-dimer levels in advanced breast carcinoma ranged from 0.4-1.0 mg/l. Further, patients with positive lymphovascular invasion showed mean plasma D-dimer levels of 0.5 mg/l. Thus one can assume that preoperative value of plasma D-dimer of 0.4 mg/l or more signified advanced breast cancer probably with local lymphovascular invasion.

DISCUSSION

Plasma levels of D-dimer was elevated in cancer patients. Fibrin cascade and extrinsic coagulation system got activated when a tumour grew, invaded and metastasised.[8]

Prognostic factors have important implications for both the patient as well as the doctor. In the present study, we attempted to find the association of various histopathological findings with levels of D-dimer as a prognostic marker.

The mean age of presentation was 51.9 years comparable with Bhavesh et al who reported a mean age of 51.6 years.[9] Our study further showed a progressive increase in the values of D-dimer as the stage of the cancer increased, in conjunction with studies by Bhavesh et al and Ghadhban.[9,10]

An increase in tumour size did not show statistically significant elevation in D-dimer values. A study by Harish et al also showed similar results where increase in tumour size did not correlate with rise in plasma D-dimer levels.[11]

There was no significant relationship between D-dimer and histologic grade of the tumour. Similar results were reported in a study conducted by Rajendran et al.[12]

80% of the patients had axillary lymph node involvement in their histopathology report and their D-dimer values were raised with statistically significance. Similar results were obtained seen in studies conducted by Ghadhban and Blackwell et al.[10,13]

Lymphovascular invasion established local and distant recurrence. When cancer cells migrated to a distant site, they established a new blood supply at the distant site. Fibrin remodelling played an important role in new vessel formation.[9] Our study showed statistically significant elevated D-dimer level in patients with lymphovascular invasion similar to reports by numerous other studies.[9,10,13] This strengthened the possibility of using D-dimer as a prognostic tool in breast cancer.

Our study was a single institute based study with small sample size. A large multicentric study with D-dimer levels in preoperative, postoperative and post adjuvant therapy setting will further validate our results.

CONCLUSION

Plasma D-dimer level is a good prognostic tool for breast cancer. Due to the ease with which plasma D-dimer levels can be obtained and its cost effectiveness, it can be added to models for predicting various parameters in breast cancer, that is, clinical stage, lymph node involvement and lymphovascular invasion.

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