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Original research article

Comparison of plasma d dimer levels in various stages of operable carcinoma breast

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Abstract

Background: Breast cancer is the most common cancer in women. There are innumerable studies pointing towards the relationship between hypercoagulability and malignancy. D dimer is one such indicator of activated coagulation system in human body.This study is an attempt to establish the role of D dimer as a prognostic marker and predictive factor for histopathologic parameters in carcinoma breast.
Methods: Analytical cross sectional study was conducted upon 60 patients who were admitted to Sri Guru Ram Das Institute of Medical Sciences And Research Center, Amritsar after taking informed written consent from the patient providing all the necessary information about the study. 60 cases of proven carcinoma breast with their preoperative D dimer levels measured and then operated during a period of April 2021 to July 2022.
Results: Plasma D dimer was increased in advanced clinical stage, higher histologic grade, lymphovascular invasion present. However no significant relation could be established between axillary lymph node status and D dimer levels.
Conclusions: Plasma D dimer levels were found elevated in advanced clinical stage. It can be considered as good prognostic marker of clinical stage, lymphovascular invasion, axillary lymph node status and histologic grade. It is cost effective and convenient option for predicting advanced stage in carcinoma breast.
Keywords: Breast carcinoma, D dimer, lymphovascular invasion

Introduction

Breast cancer is considered as the most common cancer in women and one of the important causes of death amongst them. The incidence of breast cancer is rising in India (22.9%) and it is 2nd most common cancer after cervical cancer.

Prognostic and predictive factors hold an important place in the management of breast cancer. The various prognostic factors that have been investigated are matrix metalloprotienases, protooncogenes, tumour suppressor genes, urokinase-type plasminogen activator (uPA), plasminogen activator inhibitor type 1 (PAI -1) and the coagulation factors like D dimer, factor 8, CRP, protein S, fibrinogen, thrombus precursor protein (TpP) [1].

There is a long history of D dimer and it's association with various malignancies and other diseases like venous thromboembolism and deep vein thrombosis. It was Trousseau who first reported about increased incidence of coagulopathies in cancer patients.D dimer is a sensitive indicator of increased fibrinolytic activity in cancer patients [2]. D dimer levels are raised in various solid cancers like prostate, cervix, breast and squamous esophageal cancer [3].

Coagulation disorders are amongst the commonest complications in cancer patients [4]. The three most important prognostic factors in operable carcinoma breast are lymph node status, primary tumor size, and tumor grade. D dimer assessment constitutes an attempt to consider a product of fibrin degradation (D dimer) as a specific marker to gauge the extent of disease in human breast cancer patients. Several studies have been done to prove this finding, correlating fibrinolytic activity associated with increased D dimer levels in cancer breast patients [5].

This study is an attempt to compare the pre-operative plasma D dimer levels in various stages of carcinoma breast and also to correlate it with various histopathologic parameters.

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Methods

Analytical cross sectional study was conducted from April 2021 to July 2022, where 60 female patients with histopathologically proven diagnosis of carcinoma breast were admitted and operated at Sri Guru Ram Das Institute of Medical Sciences And Research Center, Amritsar.Ethical clearance was taken from the Ethical Committee prior to commencement of the study. Informed consent was taken from each patient before any investigation or surgery.

Inclusion criteria: Patients with age > 18 years with FNAC/Tru-cut proven carcinoma breast were included in the study.

Exclusion criteria

All patients who had history of coagulation and bleeding disorders, co morbidities like myocardial infarction, cerebral vascular disease, bilateral breast carcinoma, recurrent breast carcinoma and other malignancies and whose data was incomplete were excluded.

Sample collection: Preoperative plasma D dimer levels were measured. A 2ml venous blood sample was taken in purple top vacutainer and sent to biochemistry lab for processing.

Method used: D dimer levels were measured by fluorescence immunoassay using finecare^{TM} FIA system. D dimer levels < 0.50 mg/l FEU (Fibrinogen Equivalent Units) were considered to be normal. Levels >0.50 mg/l were considered significant.

Preoperative D dimer levels were obtained and analyzed in patients with operable carcinoma breast. The relationship between plasma D dimer levels and various stages of carcinoma breast was determined. Preoperative plasma D dimer levels were correlated with various histopathological parameters like clinical stage, histological grade , axillary lymph node status and presence of lymphovascular invasion.

Data collected was statistically analyzed using SPSS software Version 26.0. All the observations made were supervised by senior fraternity from both the Department of Surgery and Department of Biochemistry. P value < 0.05 was considered significant.

Results

Total of 60 patients were selected in the study. The age of patients ranged from 30-70 years. Out of 60 patients, 35% were premenopausal and 65% were post menopausal. There were 48.3% patients in stage III and 51.7% patients in stage II and zero patients in stage I. (Table 1)

Table 1: Shows age group, frequency and percent

Age group	**Frequency**	**Percent**
30-40 years	9	15.0
41-50 years	15	25.0
51-60 years	18	30.0
61-70 years	16	26.7
>70 years	2	3.3
Menopausal status	**Frequency**	**Percent**
Menopausal	39	65.0
Premenopausal	21	35.0
Histological Type of Cancer	**Frequency**	**Percent**
Infiltrating carcinoma lobular type	2	3.3
Infiltrating ductal carcinoma	57	95.0
Mucinous type	1	1.7
Side of Surgery	**Frequency**	**Percent**
Left MRM	36	60.0
Right MRM	24	40.0
Total	60	100.0

In stage II (both IIa and IIb) median D dimer was 0.36 mg/l with interquartile range of 0.16-0.73 mg/l. Out of 31 patients in stage II, 11 patients (38%) had D dimer levels more than 0.5 mg/L and 20 patients (65%) had D dimer levels <0.5 mg/L.In breast cancer stage III, median D dimer was 0.55 mg/l with interquartile range of 0.38-0.80 mg/l.In stage III, out of 29 patients, 62% patients had D dimer >0.5mg/L and 35% had D dimer <0.5 mg/L. The 2 tailed p value was 0.024 which was statistically significant. The elevated D dimer levels correlated strongly with advanced stage of the disease (Chi value= 4.24; p value=0.039). This clearly indicates that D dimer levels increased with advancing stage. (Table 2)

Table 2: Comparison of D dimer level according to different clinical stages

Stages	**N**	**percentage**	**Median (IQR)**	**Mann Whitney U**	**p value**
Stage-II	31	51.7	0.36(0.16-0.73)	297.500	0.024

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Stage-III	29	48.3	0.55(0.38-0.80)		

When histological grade of the disease was compared, there was an elevation of D dimer levels with increase in the grade. In SBR Grade II, D dimer >0.5mg/dl was found in 3 patients (10%) and <0.5 mg/dl was found in 10 cases (32%). In SBR grade III, raised D dimer was found in 26 patients (90%) and D dimer <0.5 mg/dl was found in 21 patients (68%). p value was calculated using chi square test which was 0.040 (statistically significant).The correlation coefficient was 0.373 which tells that there was positive statistical dependence between D dimer levels and histologic grade in carcinoma breast.(Figure1)

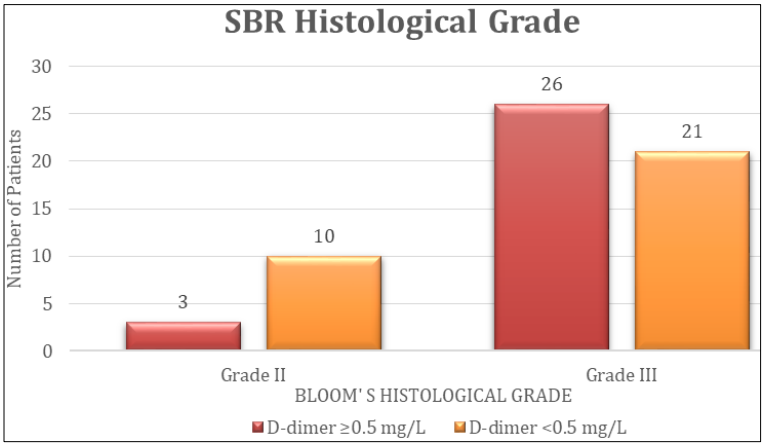

Fig 1: Comparison of D dimer according to histologic grade of tumour

D dimer level > 0.5 mg/l and LVI positive was seen in 25 cases (86%) and LVI absent in 4 cases (14%). D dimer <0.5mg/l was seen in 15 patients with LVI absent (48%) and 16 patients with LVI present (52%).The values were compared using chi square test and p value was 0.005 which was statistically significant. There is a positive correlation coefficient of 0.315 between D dimer levels and LVI in carcinoma breast cases. (Figure 2).

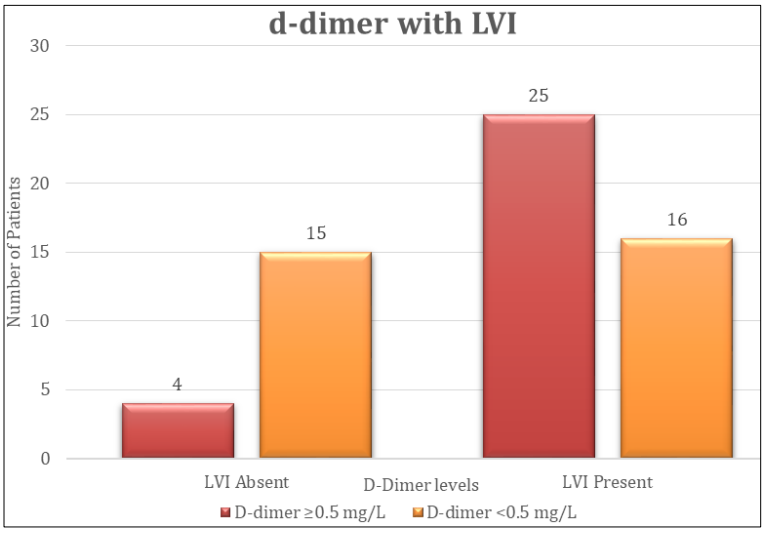

Fig 2: Comparison of D dimer levels according to lymphovascular invasion

Positive axillary lymph nodes were present in 36 patients i.e. 60% patients with median value of D dimer being 0.52 with IQR of 0.27-0.74. Significantly elevated D dimer levels were present in 19 patients (65%) with positive axillary lymph node metastasis and 10 patients (34.48%) with no lymph node metastasis. D dimer <0.5 mg/l were found in 17 patients (54.84%) with positive axillary lymph node metastasis and 14 patients (45.16%) with no lymph node metastasis. The p value was 0.440 which was statistically insignificant in this study. There is a positive correlation coefficient of 0.117 between D dimer levels and axillary lymph node metastasis in carcinoma breast cases. (Figure 3).

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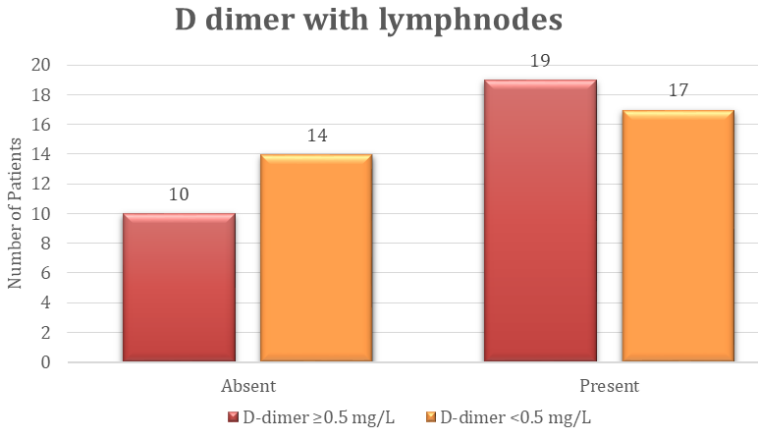

Fig 3: Comparison of D dimer according to axillary lymph node status

Discussion

Coagulation system is activated in malignancy. Fibrin formation and removal is a continuous process during development of malignant tumour [6]. D dimer is a fibrin degradation product, a small protein fragment that is generated by proteolytic activation of plasmin. It is not normally present in human blood plasma. Elevated levels of D dimer have been correlated with an enhanced stage of the disease and reduced overall survival in metastatic breast cancer [7].

In the present study, we have made an attempt to compare the levels of plasma D dimer in various stages of operable carcinoma breast which will help to establish the prognostic value of D dimer in predicting lymph node status, lymphovascular invasion and metastasis.

In this study maximum patients were in the age group of 51-60 years i.e. 30% (18 patients) followed by 27% in 61-70 years group. In a study by Momenimovahed *et al.* [8] maximum patients were in the age group of 45-49 years i.e.1052 followed by 881 patients in age group 40-44 years. The study concluded that age more than 50 years, late age of menopause and late age of first childbirth were major risk factors for developing carcinoma breast. The findings of these studies were consistent with the findings of our study.

In our study it was found that as the clinical stage progressed, the levels of D dimer rises sequentially. There was statistically significant relation between clinical stage and D dimer levels (p value 0.039). Similar findings were reported by Gadhban *et al.* [9] and Bhavesh *et al.* [10].

There was significant relation between elevated D dimer levels and higher histologic grade (p value 0.040). The findings were consistent with the study done Sringeri *et al.* [11] and Hermansyah *et al.* [12].

Lymphovascular invasion helps establish the chance of finding local and distant metastasis. For a tumour to successfully metastasize, it has to first invade the lymphatic or vascular lumen and then is transported to a new site before establishment of viability in target tissues. Usually fibrin forms around circulating tumour cells that promote microvascular entrapment needed for metastasis. Lymphovascular invasion was found in majority of patients with elevated D dimer levels (p value =0.005). Similar findings were reported by Shaker *et al.* [13] and Sringeri *et al.* [11].

In this study the relationship between axillary lymph node status and D dimer levels was found to be statistically insignificant (p value 0.440). Studies done by Patel *et al.* [14] and Batschauer *et al.* [15] were in agreement with our study.

The present study was single institute based study with small sample base. Therefore to overcome the limitations of this study, a large multicentric study with D dimer levels in preoperative, post operative and post adjuvant therapy setting will further validate our results.

Conclusion

Plasma D dimer level is a good prognostic tool for carcinoma breast. Owing to its various properties like being an affordable test, non invasive and also given the ease with which it can be obtained, it can be used to predict various parameters in breast cancer like clinical stage, histologic grade, lymphovascular invasion and axillary lymph node status.

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Conflict of interest: None declared

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Ethical approval: The study was approved by the Institutional Ethics Committee

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