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Correlation of coagulation markers with axillary lymph node metastasis in breast malignancy: a tertiary care centre study in North India

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ABSTRACT

Background: Breast cancer is the most common female cancer worldwide representing nearly a quarter (25%) of all cancers. Search for a marker which can predict lymph node metastasis in clinically negative axilla has been a matter of research for long. The present study is an attempt to evaluate role of coagulation makers with special reference to D-dimer and factor 7 and 8 in patients of carcinoma breast in predicting lymph node metastasis in carcinoma patients. Methods: The study was a prospective study conducted in 50 diagnosed patients of carcinoma breast in whom D dimer levels and factor 7 and 8 levels were measured at the time of commencement of the treatment and at six weeks

Results: Most of the patients in the study group were in the age group 41-70 (80%) years. 22% patients were of early Breast cancer. The reduction in D-dimer, factor VII and factor VIII value after 6 weeks of surgery were significant (p value 0.0001 for all three).

Conclusions: D-dimer and factor VII were found to be an independent predictive factor for lymph node metastatsis, thus providing as a safe, easy, objective and convenient supplement to sentinel node biopsy in assessing metastatic disease in axilla. Combined- with other biomarkers, it may prove to be an alternative to sentinel node biopsy in assessing metastatic disease in axilla. Significant postoperative decrease in D-dimer, factor VII and factor VIII may provide objective criteria to assess completion of surgery.

Keywords: D-dimer, Factor 7, Factor 8, Breast malignancy

INTRODUCTION

Breast cancer is the most common female cancer worldwide representing nearly a quarter (25%) of all cancers with an estimated 1.67 million new cancer cases diagnosed in 2012. Women from less developed regions (883 000 cases) have slightly more number of cases compared to more developed (794,000) regions. In India, although age adjusted incidence rate of breast cancer is lower (25.8 per 100,000) than United Kingdom (95 per 100,000) but mortality is at par (12.7 vs17.1 per 100,000) with United Kingdom. There is a significant increase in the incidence and cancer- associated morbidity and mortality in Indian subcontinent as described in global and Indian studies. Breast cancer projection for India during time periods 2020 suggests the number to go as high as 1797,900.1-5 Earlier cervical cancer was most common cancer in Indian woman but now the incidence of breast cancer has surpassed cervical cancer and is leading cause of cancer death, although cervical cancer still remains most common in rural India.

The involvement of the axillary lymph nodes (LNs) is the most important prognostic factor for recurrence in the early stages of breast cancer according to the literature. Patients with cancer- positive LN have been reported to have a four to eight times higher mortality rate in comparison to patients with negative lymph nodes. There is also a direct correlation of positive LN status with the risk of distant recurrence.

In patients with negative LN, tumor size is an independent prognostic factor of breast recurrence. Tumor grade has also been widely accepted as a prognostic factor. Histologically, tubular, mucinous, tubulolobular, and cribriform breast tumors have the best prognoses. Ductal, lobular solid, and mixed-type (ductal and lobular) tumors have a 10-year Overall Survival in only 50% of cases.⁶

The current standard surgical procedure for the management of invasive breast cancer is the complete removal of the cancer with total axillary clearance. However, recently, selective sentinel lymph node mapping and biopsy is gaining acceptance as a useful and accurate staging procedure, as it is minimally invasive.

However, some important issues, such as the optimisation of the technique for the intraoperative identification of the Sentinel lymph node, the role of intraoperative frozen section examination of the sentinel lymph node, and the clinical implications of sentinel lymph node metastasis as regards the surgical management of the axilla, still require further confirmation. Therefore, search for a maker which can predict lymph node metastasis in clinically negative axilla has been a matter of research for long.

There are studies suggesting that the coagulation and fibrinolysis activation observed in cancer patients is associated with the stage of cancer as well as with the prognosis of the patients.7 In various studies it has been shown that the disease, which is the result of an activated coagulation system, has an aggressive course, and the increasing coagulation markers may have prognostic significance.⁸ It is reported that various abnormalities including thrombocytosis, an increase in fibrinogen and fibrin degradation products like D-dimer, a rise in factors 5,7,8,9 and 11 levels and a decrease in antithrombin 3, are seen in the cancer patients. The present study is an attempt to evaluate role of these coagulation makers with special reference to D-dimer and factor 7 and 8 in patients of carcinoma breast in predicting lymph node metastasis in carcinoma patients and their relation with other known risk factors of lymph node metastasis and to look for relationship of these makers with histopathology parameter which are known to have predictive and prognostic value in carcinoma breast.

Aims and objectives

The aims and objectives of the study were to correlate plasma level of coagulation markers (D-dimer and factor VII &VIII) with clinical stage of breast cancer, to assess correlation of coagulation markers (D-dimer and factor VII & VIII) with axillary lymph node metastasis and to

assess role of coagulation marker (D-dimer and factor VII and VIII) value as a predictive marker for lymph node metastasis in breast cancer.

METHODS

A prospective study was conducted in the Department of Surgery from august 2018 to august 2019 in collaboration with Department of Pathology, Department of Radio Therapy & Radiation Oncology, at Moti Lal Nehru Medical College and Associated SRN Hospital and at Kamla Nehru Memorial Hospital, Prayagraj.

Study population

Fifty patients with diagnosed cancer breast who were admitted in SRN hospital and Kamla Nehru Memorial Hospital. All diagnosed patients of carcinoma breast were included in the study. Patients with Severe blood coagulation disorders, condition known to increase coagulation marker levels like disseminated intravascular coagulation, myocardial infarction, leukemia, thromboembolic events and recurrent cases of post operated breast malignancy were excluded from study.

The following variables were studied age of patients, TNM stage of patients, D-dimer levels, factor 7 and 8 levels, histopathology characteristics: (presence or absence of invasive carcinoma, tumour size, mitotic index, histology grade) and axillary lymph node status.

D-dimer levels were measured at time of commencement of treatment and after six weeks of surgery. The D-dimer levels was measured using card D-dimer single test which is an in vitro test for rapid determination of the fibrin degradation product D-dimer in plasma.

Statistical analysis

Analysis was performed using SPSS version 20. Statistical package for windows (SPSS, Chicago, Illinios). Categorical data were compared using Person's Chi-square test while Fisher's Exact test was used to analyze data where cell frequency was small (<5). Spearman correlation coefficients were used to examine the association between pairs of variables.

RESULTS

Age distribution of patients

Age of patients varied from 28 to 71 years. Most of the patients (70%) in the study group were in the age group 41 to 70 (80%) years and only 1 patient (2%) was above the 70 years while only 1 (2%) was less than 30 years.

Distribution of patients as per stage of disease

22% patients were of early breast cancer with none of patient in stage 1 disease. 78% patients were of locally advanced and advanced breast cancer.

Table 1: TNM stage and baseline levels of D-dimer, factors VIII and factor VII.

Stages		D-dimer baseline	Factor 8 baseline	Factor 7 baseline
	N	7	7	7
II A	Mean	535.71	373.36	366.90
	SD	125.546	116.261	126.528
	N	4	4	4
II B	Mean	373.25	447.25	446.08
	SD	120.978	105.522	62.212
	N	16	16	16
III A	Mean	542.50	420.13	409.73
	SD	197.535	107.742	88.408
	N	19	19	19
III B	Mean	501.79	426.97	436.43
	SD	196.267	141.029	108.620
	N	3	3	3
Me	Mean	836.67	562.40	537.00
	SD	316.596	154.787	66.340
	N	1	1	1
IV	Mean	1080.00	545.50	690.00
	SD	#		#
Total	N	50	50	50
P value		0.006	0.346	0.031*

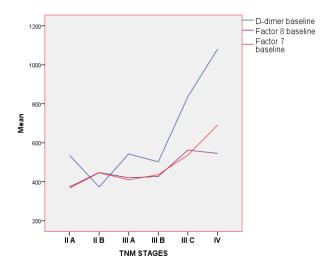


Figure 1: Observation of the lines-trend for interpretation about the relationship between stage of breast malignancy and the dependents.

Changes in levels of D-dimer, factor VIII and factor VII with advance stages of breast cancer

Table 1 summaries change in levels of D-dimer, factor 8 and factor 7 with advancing stages of the disease. The increase in the mean value of D-dimer and factor VII with advancing stage was found to be significant and non-significant for factor VIII (p=0.006 for D-dimer, 0.346 for factor VIII and 0.031 for factor VII) suggesting relation of these marker with tumor load of these marker with tumour of patient.

Changes in D-dimer value after surgery

The reduction in D-dimer value after 6 weeks of surgery are significant for D-dimer (p=0.0001) as shown in Table 2

Table 2: Baseline and post-surgery after 6 weeks Ddimer value.

		Mean	SD	P value	
	D-dimer baseline	540.94	217.237		
Pair 1	D-dimer after 6 weeks of surgery	264.28	105.130	0.00001*	

Change in level of factor VIII after surgery

The reduction in factor VIII value after 6 weeks of surgery are significant (p=0.00001) as shown in Table 3.

Table 3: Baseline and post-surgery after 6 weeks value of factor VIII.

		Mean	SD	P value
	Factor 8 baseline	429.40	126.640	
Pair 1	Factor 8 after 6 weeks of surgery	236.56	61.392	0.00001*

Change in levels of factor VII after surgery

The reduction in the value of factor VII after surgery are significant (p value 0.0001).

Table 4: Baseline and post-surgery after 6 weeks value of factor VII.

		Mean	N	SD	P value
	Factor 7 baseline	432.13	50	108.972	
Pair 1	Factor 7 after 6 weeks of surgery	246.36	50	58.059	0.0001*

Correlation between tumor size and D-dimer baseline values

Correlation value of 0.155 was obtained suggestive of significant increase of D-dimer value with increase in tumor size (Pearson's correlation).

Correlation between tumor size and factor VII and VIII baseline

Coefficient of correlation 0.217 suggestive of increase in level of baseline levels offactor VII with tumor size was

obtained and coefficient of correlation obtained in case of factor VIII was 0.199 which was significant.

Change in levels of D-dimer, factor VIII and factor VII with histological grade

Table 5 summaries change in levels of D-dimer, factor 8 and factor 7 with histological grade. The increase in the mean value of D-dimer, factor VII and factor VIII with increasing histological grade found to be insignificant

(p=0.396 for D-dimer, 0.820 for factor VIII and 0.389 for factor VII).

According to mitotic index

The difference between mean values of factor VIII according to mitotic index was significant (p=0.016) the difference between mean values of D-dimer and factor VII according to mitotic index was not significant (p=0.855 and 0.058 respectively).

Table 5: Histological grade and baseline levels of D-dimer, factors VIII and factor VII.

Histologic grade		D-dimer baseline	Factor 8 baseline	Factor 7 baseline
I	N	14	14	14
	Mean	592.14	424.43	420.66
	SD	140.941	120.789	120.556
	N	19	19	19
п	Mean	488.05	412.91	414.26
111	SD	238.124	102.104	103.461
	N	17	17	17
III	Mean	548.47	440.15	461.13
111	SD	245.764	159.951	99.991
P value		0.396	0.820	0.389

Table 6: Lymph node status and baseline levels of D-dimer, factors VIII and factor VII.

LN status		D-dimer baseline	Factor 8 baseline	Factor 7 baseline
	N	21	21	21
N0	Mean	479.05	341.62	346.00
	Std. deviation	195.087	67.728	79.886
	N	5	5	5
N1 (1-3)	Mean	454.00	466.24	491.40
	Std. deviation	105.736	111.742	51.442
	N	16	16	16
N2 (4-9)	Mean	478.94	472.90	466.16
	Std. deviation	166.847	93.828	85.645
	N	8	8	8
N3 (10 or more)	Mean	772.25	567.78	500.04
	Std. deviation	168.613	58.742	53.441
P value		0.001*	0.00001*	0.00001*

Change in levels of D-dimer, factor VIII and factor VII with lymph node status

Table 6 summaries change in levels of D-dimer, factor 8 and factor 7 with LN status. The increase in the mean value of D-dimer, factor VII and factor VIII with increase LN status found to be significant (p=0.001 for D-dimer, 0.00001 for factor VIII and 0.00001 for factor VII.

DISCUSSION

Breast cancer, has captured the attention of Surgeons throughout the ages. Despite centuries of theoretical meandering and scientific inquiry, breast cancer remains

one of the most dreaded of human diseases. Prognostic factors have important implications for both the patient with breast cancer and for her medical attendant. The major arguments relating to prognostic factors are their interrelationships and relative importance.

Prognostic factors can be determined by statistical analysis of the various clinical and pathological features of a group of patients with breast cancer. There is some discrepancy relating to the relative importance of prognostic features between studies, although most show that axillary nodal disease, tumor size, and differentiation are the most important.

A new factor will deserve inclusion as standard care only if statistical analysis of a prospective study shows that it exhibits clinical utility beyond the standard parameters. Attention is turning from prognostic factors to the search for predictive factors that will identify the tumor most likely to benefit from a specific therapy. Newer molecular markers are being searched and investigated for breast cancer prognosis assessment and prediction of therapy response including selection of best possible treatment modality.

In the present study, we also attempted to find variables which can be used to predict lymph node metastasis in node negative breast cancer (clinically N0).

Relationship with stage

Our study showed that there is progressive increase in mean baseline values of D-dimer, factor VII levels as the stage of disease progresses. This increase is found to be statistically significant. However, the increase in baseline levels of factor VIII was not statistically significant. Our results in relation to values of D-dimer are in accordance with studies done by Khangarot et al, Dirix et al, Yigit et al, Blackwell et al and Khan et al, although there has not been any previous study which compared factor VII levels with the stage of disease.⁹⁻¹³

Relationship with histological characteristics

There was no statistically significant difference found between either D-dimer or factor VII & VIII levels according to increase in tumor size. Similar results were also seen in another study done by Choudhary et al. 14 In contrast to our result, Blackwell et al showed a significant correlation between tumor size and D-dimer levels. 12 This may be because of the greater sample size in their study group and the large variance possible in mean tumor size. We did not find any significant relationship between D-dimer, factor VII and factor VIII levels and histologic grade of the tumor. Similar results were reported by other studies when D dimer and factor 'VIII levels were compared with histologic grade of tumor. 14 No any previous study had compared factor VII levels with the tumor size of histological grade of disease.

We found significant relationship between D-dimer and Factor VII and VIII levels and number of lymph nodes involved pathologically. Our study further confirms the similar findings of other studies done by Khangarot et al, Choudhary et al, Yigit et al and Blackwell et al. ^{9,11,12,14} Yigit et al showed this relationship to be significant only when number of lymph nodes is more than 10. ¹¹ As axillary lymph node involvement is most important prognostic factor, this relationship inspires confidence in suggesting D-dimer along with factor VII and VIII levels as prognostic factors, further these factors may be used in those patients who are node negative for an individualized assessment and use of systemic therapy.

Post-surgery changes

We found significant decrease in levels of D-dimer, factor VII and factor VIII after the patients underwent surgery indicating relationship of these markers with tumor load. None of the previous studies compared factor VII levels after surgery. This reduction in D-dimer, factor VII and factor VIII may be used as a standard value to assess completion of surgery in operable breast cancer and suggests its utility as tumor markers for early detection of recurrence of disease.

Predictive factors for lymph node metastasis

In our study clinicopathological parameters for lymph node metastasis showed that Mitotic index, baseline factor VII and baseline D-dimer value were statistically important predictive factors for lymph node metastasis. Blackwell et al showed elevated D-dimer and tumor size as significant markers for predicting lymph node metastasis in breast cancer. ¹² Although none of previous studies have included baseline factor VII levels in their study model to predict lymph node metastasis.

D-dimer as predictor of lymph node metastasis

Though our study, in a first attempt and previous study showed a significant correlation of D-dimer and factor VII to predict lymph node metastasis, it definitely provides optimism and highlights the need of large prospective trials to substantiate these findings.

Studies have shown that the 5-year survival for patients with node-negative disease is 82.8% compared with 73% for 1-3 positive nodes, 45.7% for 4-12 positive nodes, and 28.4% for >13 positive nodes. These data demonstrate that the risk of recurrence is significant enough with lymph node positive disease to warrant adjuvant systemic therapy since, generally, a future risk of distant recurrence of 20% or greater is regarded significant enough to consider the risks of therapy. Although the ability of an experienced surgeon to accurately stage the axilla with sentinel node biopsy is accepted, multiple questions remain, including the most suitable method to identify the sentinel node as well as the optimal pathologic method to assess the sentinel node for involvement. D-dimer may prove 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. Moreover, D-dimer in combination with other biomarkers like factor VII and VIII also provides an alternative to conventional sentinel node biopsy to assess metastatic disease in axilla.

This study highlights that D-dimer along with factor VII and factor VIII seems to be a promising biomarker in this group of patients, it definitely requires further prospective

studies with long term follow up to make any recommendation.

CONCLUSION

D-dimer, factor VII and factor VIII levels may be used as standard for systemic adjuvant therapy in node negative breast cancer. D-dimer may prove 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. Moreover D-dimer alone or in combination with other biomarkers may also provide an alternative to conventional sentinel node biopsy to assess metastatic disease in axilla. Significant postoperative decrease in D-dimer, factor VII and factor VIII may provide objective criteria to assess completion of surgery. Further these findings need to be validated with large, multicentric prospective studies with long term follow up.

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Institutional Ethics Committee

REFERENCES

- 1. Porter PL. Global trends in breast cancer incidence and mortality. Salud Pública de México. 2009;51:141-6.
- 2. Babu GR, Lakshmi SB, Thiyagarajan JA. Epidemiological correlates of breast cancer in South India. Asian Pac J Cancer Prev. 2013;14:5077-83.
- 3. Ali I, Wani WA, Saleem K. Cancer scenario in India with future perspectives. Cancer Therapy. 2011;8:56-70.
- 4. Srinath Reddy K, Shah B, Varghese C, Ramadoss A. Responding to the threat of chronic diseases in India. Lancet. 2005;366:1744-9.
- 5. Balasubramaniam S, Rotti S, Vivekanandam S. Risk factors of female breast carcinoma:a case control study at Puducherry. Indian J Cancer. 2013;50:65-70.

- 6. Galea MH, Blamey RW, Elston CE, Ellis IO. The Nottingham prognostic index in primary breast cancer. Breast Cancer Research and Treatment. 1992;22(3):207-19.
- 7. van Duijnhoven EM, Lustermans FA, van Wersch JW. Evaluation of the coagulation/fibrinolysis balance in patients with colorectal cancer. Haemostasis.1993;23:168-72.
- 8. Beer JH, Haeberli A, Vogt A. Coagulation markers predict survival in cancer patients. Thromb Haemost. 2002;88:745-9.
- Khangarota SS, Guptab N, Goswamic B, Hadkea NS, Lala P, Guptad N, et al. Correlation of D dimer and factor VIII levels with histopathology in patients with breast carcinoma. Cancer Biomark. 2010;7:305-14.
- Dirix L, Salgado R, Weytjens R, Colpaert C, Benoy I, Huget P, et al. Plasma fibrin D-dimer levels correlate with tumour volume, progression rate and survival in patients with metastatic breast cancer. Br J Cancer. 2002;86:389-95.
- 11. Yigit E, Gonullu G, Yucel I, Turgut M, Erdem D, Cakar B. Relation between hemostatic parameters and prognostic/predictive factors in breast cancer. Eur J Intern Med. 2008;19:602-7.
- 12. 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. 2000:18:600-8.
- 13. Khan MZ, Khan MS, Raziq F, Khattak AM. Fibrinogen degradation products and d- dimers in patients with breast carcinoma. Gomal J Med Sci. 2007;5(1):9-12.
- 14. Choudhary GS, Bairwa MS, Choudhary A, Singodia R. Correlation of coagulation markers with axillary lymph node metastasis in carcinoma breast. J Evol Med Dent Sci. 2017;6(91):6449-53.

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