A Study of Correlation of Pre-operative Serum CA-15.3 with Respect to Prognostic Factors and Early Recurrence in Breast Carcinoma in A Tertiary Care Centre in India

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ABSTRACT

Introduction: There is a huge list of prognostic markers in breast cancer but the availability of a circulating prognostic factor, which is cost effective, especially fit to provide independent data and was prognostic would be of value in breast cancer. The study was aimed to correlate serum CA 15.3 levels at the time of presentation with various other prognostic markers like tumour size, Nodal status, TNM staging, ER,PR and Her2/neu status, HPE report of tumour metastasis, early recurrence within one year and whether it can be used as a prognostic marker, indicator for tumour aggressiveness and recurrence .

Material and methods: It was an institution based, prospective observational study in a tertiary care centre. Study was conducted on patients who attended the department of General Surgery at Medical College Kolkata. The Pearson correlation test was used to examine association between parametric variables and Serum CA 15.3 levels and Spearman's Rank Correlation test was applied to check association of all non-parametric variables.

Results: Serum CA 15.3 Levels correlated highly significantly with size of breast tumor, metastasis and clinical staging and significantly and with T-Stage and Nodal Status all having a positive correlation. Serum CA 15.3 Levels also correlated highly significantly with histological Grade and lymphovascular invasion and recurrence at one year with a positive correlation. Serum CA 15.3 levels however had negative correlation with age of the patient.

Conclusion: CA 15.3 can be used as diagnostic and prognostic marker in the most common carcinoma i.e ductal carcinoma of breast.

Keywords: Co-relation Pre-operative, CA-15.3, Prognostic Factors, Recurrence

INTRODUCTION

Breast cancer is the most common site-specific cancer in women and is the leading cause of death from cancer for women aged 20-59 years. It accounts for 26% of all newly diagnosed cancers in females and is responsible for 15% of the cancer-related deaths in women.[1]

A prognostic factor is any measurement available at or before the time of surgery that correlates with disease-free or overall survival in the absence of systemic adjuvant therapy and, as a result, is able to correlate with the natural history of the disease.[2]

There is a huge list of prognostic markers in breast cancer, however, the International Consensus Panel of St.Gallen determined the standard prognostic factors of breast cancer as follows: lymph node status, tumour size, histological grade, estrogen/progesterone receptor status (ER/PR) and age).[3] Additional important factors according to NCCN guidelines are tumour HER2/neu status, multi gene testing like OncotypeDx or Mammaprint, presence or absence of detectable metastasis, patient's comorbid conditions and menopausal status[4]

Existing histologic (tumour size, tumour grade, and axillary node status) and biological [e.g., urokinase plasminogen activator, plasminogen activator inhibitor-1 (PAI-1), 6cathepsin D, and HER-2neu], prognostic factors for breast cancer all require tumour tissue. Clearly, the availability of a circulating prognostic factor, which is cost effective, especially fit provided independent data and was prognostic within subgroups defined by traditional criteria, would be of value in breast cancer.[5]

Tumour markers are molecules that may be present in higher than usual concentrations in the tissue, serum, urine, or other body fluids of patients with cancer. Serum tumour markers may aid cancer diagnosis, assess prognosis, guide choice of treatment, monitor progress during and after treatment, and/or be used as screening tests.[6]

Circulating tumour marker as Cancer Antigen 15-3 (CA 15-3) has become well established diagnostic tools as fast, non-invasive, reproducible and quantitative parameters in follow-up care and monitoring therapy of breast cancer patients. According to current ASCO guidelines CA 15-3 can be used only for monitoring patients with metastatic disease during active therapy, in conjunction with diagnostic imaging, history,and physical examination and not recommended for screening, diagnostic or prognostic purpose.[7]

CA 15-3, the most commonly used serum tumour marker in breast cancer,is the product of MUC-1 gene, and mucins are

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How to cite this article: Chandan Roy Choudhary, Neha Agarwala. A study of correlation of pre-operative serum CA-15.3 with respect to prognostic factors and early recurrence in breast carcinoma in a tertiary care centre in India. International Journal of Contemporary Medical Research 2018;5(10):J8-J12.

DOI: http://dx.doi.org/10.21276/ijcmr.2018.5.10.12

aberrantly overexpressed in many adenocarcinomas in an under-glycosylated form and then shed into the circulation. Therefore, higher level of CA 15-3 may be associated with larger burden of occult disease and poor outcome. There have been many reports showing worse prognosis in patients with high concentration of CA 15-3, and CA 15-3 has been shown to be an independent predictor of first recurrence as well as a powerful prognostic indicator in patients with advanced breast cancer. Despite poor prognosis associated with an initially high value, scientific societies have not yet recommended its determination in the initial evaluation as regards the extent of disease.[8,9,10]

Therefore, it is thought worthwhile to evaluate the prognostic significance of this marker. The purpose of present work is to check the correlation of CA 15-3 values with other established prognostic factors like tumour grade, tumour size, lymph node status, hormone receptor status, her2 neu status and early recurrence(within one year) in Indian women.

The standard cut-off value for raised CA 15.3 levels according to most studies is 30 U/ml.[10,11] It would be of value to see whether CA 15.3 levels are prognostically significant at lower value i.e. between 20-30 U/ml too and whether the cut-off value for CA 15.3 levels as a prognostic marker should be lowered.

Study was aimed to follow the clinic-pathological presentations of patients with diagnosed breast carcinoma and their correlation with different prognostic markers and to correlate correlate serum CA 15.3 levels at the time of presentation with various other prognostic markers like tumour size, Nodal status, TNM staging, ER,PR and Her2/neu status, HPE report of tumour, early recurrence within one year and to analyse the data and evaluate if serum CA 15.3 level can be used as a prognostic marker and indicator for tumour aggressiveness.

MATERIAL AND METHODS

It was a institution based, prospective observational study in a tertiary care centre. Study was conducted in Department of General Surgery, Medical College, Kolkata, India. Patients of any age coming to Medical College (OPD or Emergency) with biopsy proven Infiltrating Ductal Carcinoma of breast at preoperative stage. Study was done in June 2016 – June 2018. Sample size was 50. Ethical Clearance was obtained from institutional ethical committee and written consent taken from all patients before the start of study.

Inclusion Criteria

Patients of any age coming to Medical College with biopsy proven Ductal Carcinoma of breast at preoperative stage.

Exclusion Criteria:

a. Male breast Cancer
b. Patients already undergone surgery for breast carcinoma.
c. Patients with any other cancer present simultaneously.
d. Patients who have received neoadjuvant chemotherapy, radiotherapy or endocrine therapy.
e Lobular carcinoma of breast.
f. Patients with coexisting or history of benign breast disease.

Parameters studied

a) TNM staging of the breast cancer patients under study.
b) Histopathological examination of post-mastectomy specimen using formalin-fixed, paraffin-embedded, haematoxylin and eosin stained slides representing invasive component of tumour to evaluate, histological grade and lymphovascular invasion.
c) ER/PR status and HER-2/net positivity by enzyme immunoassay.
d) Preoperative Serum Ca 15.3 levels.
e) Post operative follow up for 1year - clinically, radiologically and pathologically to determine early recurrences (for as many cases possible)
f) Study of all the above factors (a) to (f) statistically

Study techniques

i. All cases of female breast carcinoma fulfilling inclusion and exclusion criteria were subjected to a detailed history using a structured questionnaire and examined clinically.
ii. Preoperative Serum CA 15.3 levels estimated by Chemiluminescent Microparticle Immunoassay and a value of >=30 U/ml was considered to be raised.
iii. TNM staging was done according to clinical findings.
iv. Histopathological examination of the specimen was done to evaluate histological grade (by modified Scarff-Bloom-Richardson system) and lymphovascular invasion.
v. Hormone receptors (ER/PR) were also determined by immunohistochemistry method using rabbit monoclonal antibody (ER- clone SP1, PR- clone SP2, Labvision USA) from paraffin-embedded histopathology specimen. ER and PR positivity was defined as the presence of 10% or more positively stained nuclei in ten high-power fields.
vi. The intensity of HER-2/neu membrane staining was scored as 0, 1+, 2+ or 3+ (according to standardization of the particular laboratory concerned).
vii. After the patients evaluated, were anaesthetically fit for surgery, modified radical mastectomy with axillary lymph node resection was done. Some patients were offered surgery after neoadjuvant therapy.
viii. Patients were followed up(as many cases possible) for 1year to detect any signs of recurrence.
ix. Then all these parameters were correlated statistically.

STATISTICAL ANALYSIS

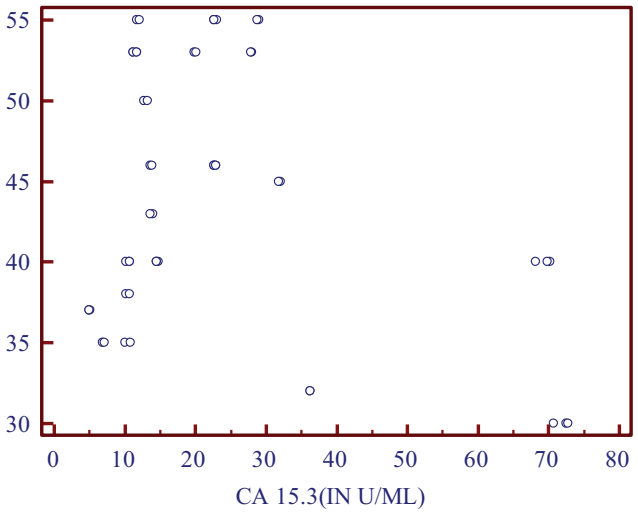
All statistical analyses were performed with IBM SPSS Statistics software version 22.0 for Windows. The Pearson correlation test was used to examine association between all continuous parametric variables and Serum CA 15.3 levels. Spearman's Rank Correlation test was applied to check association of all non-parametric variables with Serum CA 15.3 levels. All bi-variate analysis was appropriately done and p value < 0.05 were considered statistically significant

RESULTS

In this study, 50 female patients suffering from breast cancer and fulfilling the selection criteria of this study were examined.

Age

In our study the mean age of the study population was 44.04 years ± 8.028 (S.D.). The range was from 30 years to 55 years. Overall 35 cases(70%) were in <=50 years age group. We can see here that more cases are there in <50 years age group which corroborates with Indian data. Young age has been associated with larger tumour size, higher number of metastatic lymph nodes, poorer tumour grade, low rates of hormone receptor-positive status, earlier and more frequent loco regional recurrences, and poorer overall survival



Graph 1 Scatter Graph with Regression line showing a negative correlation with age

Religion

In our study, 41 patients were Hindu (82%) and 9 patients were Muslims (18%). According to 2011 Census in India, the distribution of population by religion is 80.5% Hindus and 13.4% Muslims hence the religion distribution in our study can be explained by general distribution in the population and is not specific to Breast Cancer.

Affected side

In our study, 20 patients (40%) had Left sided and 30 patients (60%) had Right sided breast cancer. However according to literature, many studies have shown that unilateral Breast cancer, is more frequent in the left breast than in the right.[12] This discrepancy can be attributed to sample size in our study.

Affected quadrant

In our study, maximum i.e.29 patients (58%) had cancer in upper outer (UO) quadrant of breast which is consistent with literature. It is considered to be a reflection of the greater amount of breast tissue in this quadrant. Another hypothesis is that underarm cosmetics cause breast cancer in upper outer quadrant.[13]

Tumour size

The mean size of the breast tumour was 4.53 cm ± 2.2072 (S.D.). The range was from 1.5 to 10 cm.

		T staging	Nodal status	Metastasis (M)	Clinical Stage
Serum CA 15.3 (IN U/ML)	Spearman's rho Correlation Coefficient	.320*	.298*	.551**	.371**
	Sig. (2-tailed)	.023	.035	.000	.008
	N	50	50	50	50
*. Correlation is significant at the 0.05 level (2-tailed).					
**. Correlation is significant at the 0.01 level (2-tailed). -Highly significant					

Table-1: Correlation of Serum CA 15.3 levels Clinical stage and pTNM.

		ER Status	PR Status	HER 2 NEU Status
Serum CA 15.3 (IN U/ML)	Spearman's rho Correlation Coefficient	-.549**	-.071	.534**
	Sig. (2-tailed)	.000	.630	.000
	N	48	48	44

Table-2: Correlation of Serum 15.3 with receptor status

		Follow up (approx.1 year)
Serum CA 15.3 (IN U/ML)	Spearman's rho Correlation Coefficient	.744**
	Sig. (2-tailed)	.000
	N	37
**. Correlation is significant at the 0.01 level (2-tailed).		

Table-3: Correlation of CA15.3 with recurrence at 1 year

Stage			<20 U/mL	20-30 U/mL	Total
IIb	Follow up (approx.1 yr)	No recurrence	11	1	12
		Recurrence	0	5	5
	Total	11	6	17	

Table-4: Co-relation of recurrence over one year with CA-15.3 levels

The maximum no. of cases i.e. 28 cases (56%) presented with a tumour size in the range >2 cm - ≤5 cm. (T2 Stage). Remaining 9 cases (18%) presented with a tumour >5 cm. (T3 Stage), 7 cases (14%) at T4 Stage and only 6 cases (12%) at tumour size <2cm (T1 stage).

Node positivity and metastasis

40 cases (80%) were node positive and 10 cases (20%) were node negative.

39 cases (78%) did not have distant metastasis (M0) and 11 cases (22%) had distant metastasis(M1) at the time of detection.

Clinical staging: All the cases were clinically staged.

6 cases were diagnosed as stage IA (12.0%), 4 cases as stage IIA (8.0%), 22 cases as stage IIB (44%),7 cases as stage IIIA (14.0%) and 11 cases as stage IV (22.0%) whereas none of the cases were in stage IB, IIIB and IIIC. There were no cases of In-situ carcinoma.

In our study 88% cases were diagnoses in stage II, III or IV.

Histopathological grading and lympho-vascular invasion

All tumours were graded histologically as per Scarff-Bloom-Richardson (SBR) classification. Out of 50 patients, 9 had histological grade I tumour (18%), 19 had grade II tumour (38%) and 22 had grade III tumour (44%). Higher grade predicts poorer prognosis.

We also saw that the prevalence of high grade tumor was more in our study population as expected, since there were higher number of younger age patients (<50 years).

Lymphovascular invasion, as seen by histopathological examination of specimen was present in 23 cases (46%) and absent in 27 cases (54%). Its presence determines poorer prognosis and indicates risks of micrometastasis.

Receptor status (ER, PR and HER2 neu)

Estrogen - 31 patients (62.5%) were ER positive whereas 19 patients (37.5%) were ER negative.

Progesterone Receptor status - Out of 50 patients, 13 patients (25%) were PR positive whereas 37 patients (75%) were PR negative

Her2-neu status: 44 patients had their Her-2neu status evaluated out of which 24 were negative (negative – 16, 1+ score 5 patients and 2+ score negative by FISH- 3), 20 patients were positive for Her-2neu (2+ score positive by FISH – 3 patients, 3+ score – 17 patients). 6 patients who were 2+ score by IHC couldn't get their FISH done outside which was not available at the institute at that time.

Subtypes: Luminal- 10 Luminal B: 3 Her-2 neu + - 21 Triple-ve 10, Not evaluated fully - 6

Early recurrence (within 1 year)

Follow up could be done for 37 cases. 13 were lost in f ollow up. 25 patients (67.6%) did not have any recurrence. 12 patients (32.4%) had either local or systemic recurrence within one year of time.

Serum CA 15.3 levels

The mean value of Serum CA 15.3 levels in the study population was 23.40 U/ml ± 19.39 (S.D.). The range was from 4.9 U/ml to 72.80 U/ml. At the cut off level of 30 U/ml, 10 patients(20%) had raised tumor marker levels while the rest 40 cases(80%) were within normal limits(<30 U/ml). Amongst raised levels, maximum (4 cases, 8%) were in 30-40 U/ml range. 23 patient (46%) were having levels in range of 10-20 U/ml-most frequent range.

Correlation between Parametric variables was tested by using Pearson correlation

The Pearson correlation coefficient and p-value was calculated. Serum CA 15.3 Levels correlates highly significantly with Size of Breast Tumour with a Correlation coefficient of .371 (positive correlation) and p-value of .008 (highly significant at 0.01 level). Serum CA 15.3 Levels correlates significantly with Age of the patient with a Correlation coefficient of -.297 (negative correlation) and p-value of .036 (significant at 0.05 level).

Correlation between non-parametric variables was tested by Spearman's rho rank correlation. The Spearman's rho correlation coefficient and p-value were calculated.

Serum CA 15.3 Levels correlated significantly with T-Stage and Nodal Status and highly significantly with Metastasis and Clinical staging all having a positive correlation. (Table-1)

Serum CA 15.3 Levels correlated highly significantly with Histological Grade and Lympho-vascular invasion, both having a positive correlation.

Serum CA 15.3 Levels correlated highly significantly with ER Status and Her2/neu Status (Table-2).

ER Status has a negative correlation with Serum CA 15.3 levels whereas Her2/neu status has a positive correlation (Table-2).

PR status does not have a statistically significant correlation with Serum CA15.3 levels (Table-2).

Serum CA 15.3 Levels correlated highly significantly with incidence of recurrence within 1 year with a positive correlation (Table:3). Fisher's exact test is highly significant with p = 0.000970

Standard cut-off value of considering raised CA 15.3 levels is 30 U/ ml, but we see that in stage IIb level, even when the level of CA 15.3 is above 20 U/ml, there is considerable chance of recurrence.

Thus we can consider lowering the cut-off range to 20 U/ml (Table:4).

DISCUSSION

Serum CA 15.3 Levels correlates highly significantly with Size of Breast Tumor (p-.008), Metastasis (p-.000) and Clinical staging(p-.008) and significantly with T-Stage(p-.023) and Nodal Status(p-.035) all having a positive correlation.

This finding is supported with other studies in literature. In a study of 600 patients, CA 15-3 concentrations were significantly higher in patients with large tumors (P 0.002) and in patients with increasing nodal burden (P 0.004). Cuzick's test for trend demonstrated a significant increase in CA 15-3 across these groups for tumour size (P-0.0001) and for nodal burden (P -0.0001). Concentrations were also higher in patients who were axillary node positive compared with those who were axillary node negative (P 0.004)[14]

In another study including 368 patients, preoperative CA15-3 in patients with Breast Cancer was significantly associated with tumor size (p=0.003) and TNM stage (p=0.005). Increased CA15-3 (>30 U/ml) concentrations were more often found in patients with larger tumors (p<0.05), advanced stage (p=0.004) and node-positive disease (p=0.007)[15] Many other studies showed similar findings.[12,15,16]

Serum CA 15.3 Levels correlate highly significantly with Histological Grade (p-.002) and lymphovascular invasion (p-.000) both having a positive correlation.Similar finding are found from other studies in literature. Preoperative CA15-3 in patients with BC was significantly associated with vascular invasion (p=0.018).[14] CA 15.3 was found to be higher in higher histological grade.[15,16]

Serum CA 15.3 levels correlates highly significantly with ER Status (p-.000) and Her2/neu Status (p-000). ER Status has a negative correlation with Serum CA 15.3 levels whereas Her2/neu status has a positive correlation. PR status does not have a statistically significant correlation with Serum CA15.3 levels(p-.630) There are conflicting findings in literature, with most studies finding no correlation between CA 15.3 and various hormonal receptor status.[9,16] however some studies have found correlation.[10,11]

Serum CA 15.3 Levels has significant negative correlation with age of the patient (p- .036) (Graph-1). This finding is also contradictory to other studies in literature where they have found either a positive correlation or no correlation.[5,10] However if we see the data in our study closely, we can see that Age also has negative correlation with tumor size and stage. This means that most young patients that we had in our study are of higher stage and hence higher CA 15.3 levels.

CONCLUSION

Serum CA 15.3 has positive correlation with most of the established prognostic markers of breast cancer and also seems to be an independent prognostic marker. It can be recommended for routine use as a preoperative prognostic marker and aid in management planning such as neoadjuvant therapy and adjuvant therapy although further investigation is necessary. CA 15.3 is strong marker of metastatic disease, hence on its routine preoperative evaluation, if it is raised, can direct more detailed metastatic work up. Levels of CA 15.3 between 20-30 U/ml are significant in indicating chances of recurrence, even in early stages (IIb).

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 06-09-2018; **Accepted:** 04-10-2018; **Published:** 15-10-2018