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RESEARCH ARTICLE

Evaluating the Relationship Between CA15.3 Levels and Key Clinical Factors in Breast Cancer Patients of North East India

Sawmik Das[1], Anupam Sarma[2]*, Avdhesh Kumar Rai[3]*, Niharika Bhuyan[1], Ratnadeep Sharma[4]

[1]Department of Biochemistry, Dr B. Borooah Cancer Institute, A. K. Azad Road, Gopinath Nagar, Guwahati-781016, Assam, India. [2]Department of OncoPathology, Dr B. Borooah Cancer Institute, A. K. Azad Road, Gopinath Nagar, Guwahati-781016, Assam, India. [3]DBT Centre for Molecular Biology and Cancer Research, Dr B. Borooah Cancer Institute, A. K. Azad Road, Gopinath Nagar, Guwahati-781016, Assam, India. [4]Population Based Cancer Registry-Kamrup, Dr B. Borooah Cancer Institute, A. K. Azad Road, Gopinath Nagar, Guwahati-781016, Assam, India.

Abstract

Introduction: Breast cancer is the most common malignancy in women worldwide, with early detection crucial for improving prognosis and survival rates. Aims and objectives: This study aims to evaluate the association between serum CA15.3 levels and the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (Her2/neu) in breast cancer patients. **Materials and Methods:** Venous blood samples from 302 histologically confirmed breast cancer patients were analyzed. Serum CA15.3 levels were measured using an automatic chemiluminescence immunoassay system. Statistical analyses were conducted to assess the correlation between CA15.3 levels and hormone receptors in both bivariate and multivariate setups. **Results:** Results showed that older patients (age > 48) were over three times more likely to have elevated CA15.3 levels (OR: 3.27, 95% CI: 1.18 to 9.63). A significant association was also found between Her2/neu status and CA15.3 levels, with positive Her2/neu patients more likely to have elevated CA15.3. ER and PR statuses were similarly associated with higher CA15.3 levels, highlighting the role of hormonal factors in breast cancer. However, tumour grade did not significantly impact CA15.3 levels. The ROC curve analysis revealed moderate discriminatory power with an AUC of 0.679, indicating that the model correctly classifies approximately 67.9% of cases. The optimal threshold for predicting elevated CA15.3 levels was 0.507, yielding a sensitivity of 0.479 and specificity of 0.859. **Conclusion:** In conclusion, CA15.3 levels in breast cancer patients are significantly influenced by ER, PR, and Her2/neu status, as well as age.

Keywords: Breast Cancer- CA15.3- ER- PR- Her2neu- ROC

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Introduction

Breast cancer is the most prevalent form of cancer among women. About 1 in every 10 women will be diagnosed with breast cancer during her lifetime [1]. Breast cancer is one of the most common malignant tumours, and its incidence is increasing year by year [2]. Due to advancement in early diagnostic methods and combined modality therapies, the mortality rate of breast cancer has decreased in recent years [3, 4]. Breast cancer treatments are more effective when the disease is detected early, compared to when the initial tumour burden is advanced. The elevated serum markers in breast cancer can be useful for early diagnosis, determine prognosis, predicting response or resistance to specific therapies, post-surgery surveillance and monitoring therapy in patients with advanced disease [5].

The data from the Population based cancer registry in Kamrup district, Assam, India documented a total of 637 incidence cases of breast cancer (2012-2015). The analysis revealed a 5 year overall survival rate of 59.4% among these patients with 95% cancer incidence.

Corresponding Authors:
Dr. Anupam Sarma and Avdhesh Kumar Rai
MD, Professor and Head, Department of Pathology, Dr B. Borooah Cancer Institute, A. K. Azad Road, Gopinath Nagar, Guwahati-781016, Assam, India.
PhD, Assistant Research Officer (Scientific Officer-D), DBT Centre for Molecular Biology & Cancer Research, Dr B. Borooah Cancer Institute, A. K. Azad Road, Gopinath Nagar, Guwahati-781016, Assam, India.
Emails: dranupamsarma@gmail.com, dravdheshkumarrai@gmail.com

In our hospital based cancer registry (HBCR) a total of 275 breast cancer patients were registered and followed up over a 5 year period. Out of these, 200 patients were alive at the end of the follow up period, while 75 patients had succumbed to the disease, resulting in a mortality count of 75. The overall 5 year survival rate for breast cancer was calculated 72.7% with the mean survival time across all patients was found to be 3.1 years, reflecting the average duration of survival within the study population.

CA15.3 is a widely used serum tumour marker for breast cancer in clinical practice. CA15.3 is a non-invasive, readily available, and cost-effective tumour marker for the immediate diagnosis, monitoring and prediction of early, advanced and metastatic breast cancer. [6- 8]. Cancer antigen CA15.3 is produced by the MUC-1 gene, with mucins being abnormally overexpressed in many adenocarcinomas in an under-glycosylated form, subsequently being released into the bloodstream [9]. CA15.3 has been demonstrated to be an independent predictor of initial recurrence and a strong prognostic indicator in patients with advanced breast cancer [10]. CA15.3 levels are influenced by tumour mass but do not appear to vary based on the location of distant metastases [11]. At present, the most commonly used pathological factors include tumour size, lymph node status, tumour grade and the status of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) status [12].

Estrogen and progesterone play a crucial role in regulating the growth and differentiation of normal breast tissue, and they are significant factors in the development and progression of breast cancer [13-16]. Generally, women with tumours that are positive for both ER and PR have longer survival rates and respond better to endocrine therapy compared to those with tumours negative for both receptors. For women with discordant receptor status, survival and response are considered intermediate [17-21]. In 15%-20% of invasive breast cancers, the HER2 gene is amplified, which is strongly associated with the overexpression of the HER2 protein. HER2 amplification is a negative prognostic factor associated with increased recurrence and mortality rates, and it also predicts responsiveness to anthracycline-based chemotherapies in breast cancer patients [22, 23]. HER2/neu is a growth factor receptor gene that is amplified in roughly 20% to 25% of breast cancers with its encoded protein also present at abnormally high levels in malignant cells [22, 24, 25].

The aim of the study was to evaluate the relationship between the levels of the tumour marker CA15.3 in the serum and the status of hormone receptors (ER, PR) and the Her2/neu status in breast cancer patients. Additionally, the study evaluates the ability of the model to differentiate between elevated and non-elevated CA15.3 levels using ROC (Receiver Operating Characteristic) curve analysis.

Materials and Methods

A total of 302 blood samples of histopathologically confirmed breast cancer patients were collected at Dr. B. Borooah Cancer Institute since April 2022 to June 2023. Patient informed written consent and demographic, clinical information in proforma were obtained. All histologically confirmed cases of breast cancer patients from grade I–III and in the age range from 25-70 years were enrolled and patients have not received any prior treatment for breast cancer (such as surgery, chemotherapy or radiation).

Venous blood samples were collected from each enrolled patient in 10ml clot activator vials. Blood was then centrifuged at 3500rpm for 15minutes to separate serum samples. CA15.3 levels were measured using commercially available CA15.3 OCD kit on an automatic chemiluminescence immunoassay system as per the manufacturer's instruction (Orthodiagnostics, VITROS 5600,USA). In healthy individuals, CA15.3 levels range from 0 to 30 U/mL were considered normal and with values higher than 30U/mL considered elevated.

The immunohistochemistry for ER, PR and Her2neu was performed using Automated Ventana Benchmark system. The ER and PR results were evaluated using ALLRED scoring method. ER was detected using clone SP1 and PR using clone 1E2.

Statistical analysis

In this study, all analyses were performed using RStudio Version 1.4.1717 and the code was written in the R programming language. All analysis were conducted using both bivariate and multivariable statistical techniques to investigate the association between various factors and CA15.3 groups. Bivariate analysis was performed using the Chi-square test of association to identify significant relationships between categorical variable and the outcome variable. For the multivariable analysis we utilized the Generalized Linear Model (GLM) function from the 'stats' package in R to quantify the associations and to estimate the log-odds/odds ratios and their corresponding 95% confidence intervals. A receiver operating characteristics (ROC) curve was constructed for checking the performance of the multivariable logistic regression model. $p < 0.05$ is considered to be significant.

Results

We employed both bivariate and multivariable statistical techniques to investigate the association between various factors and the CA15.3 groups (≤ 30U/ml and > 30u/ml) , as shown in Table 1 and Table 2.

Bivariate Analysis

We conducted a Bivariate Chi-Square test of association to investigate the relationship between various factors and the CA15.3 groups (≤ 30u/ml and > 30u/ml). The factors analyzed included age, tumour grade, Her2/neu, ER and PR. Age was found to have a highly significant association with CA15.3 levels (Chi-squared= 17.741, p-value=2.53E-05). This indicates that there is a strong statistical relationship between age and CA15.3 levels, suggesting that the likelihood of having higher CA15.3 levels (>30u/ml) increases with age. This signify that older patients are more likely to present with elevated CA15.3. Her2/neu (human epidermal growth factor

Table 1. Bivariate Chi Square test of Association with CA15.3

Factor	Factor Group	CA15.3 Concentration		Chi-squared	P-value
		>30 CA15.3	<=30 CA15.3		
Age	>48	62	78	17.741	2.53E-05*
	<=48	34	128		
Grade	I	7	14	0.044	0.978
	II	67	146		
	III	22	46		
Her2/neu	Positive	68	109	7.946	0.005*
	Negative	28	97		
ER	Positive	67	108	7.406	0.006*
	Negative	29	98		
PR	Positive	56	88	5.79	0.016*
	Negative	40	118		

* represents statistically significant result at 5% level of significance

Table 2. Results of the Multivariable Logistic Model

			Confidence Interval		
Factors	Study Levels	Log-odds/ Odds Ratio	2.5%	97.5%	P-value
Age	> 48	1.18/3.27	1.95	5.58	9.63E-06*
Grade	II	-0.29/0.75	0.28	2.16	0.58134
	III	-0.34/0.72	0.24	2.24	0.55073
Her2/neu	Positive	0.69/2.01	0.58	7.11	0.27209
ER	Positive	0.13/1.14	0.33	3.96	0.84103
PR	Positive	0.09/1.09	0.51	2.40	0.82227

* represents statistically significant result at 5% level of significance

receptor 2 status also showed a significant association with CA15.3 levels (Chi-squared = 7.946, p-value = 0.005). This suggests that patients with positive Her2/neu status are more likely to have elevated CA15.3 levels. Her2/neu status is an important factor in breast cancer prognosis and treatment, indicating that CA15.3 levels might reflect tumour biology influenced by hormonal factors. ER (Estrogen Receptor status) and PR (Progesterone Receptor status) also demonstrated significant associations with CA15.3 levels (ER: Chi-squared =7.406, p-value = 0.006; PR: Chi-squared =5.790, p-value = 0.016). These findings suggest that estrogen and progesterone receptor statuses are important factors influencing CA15.3 levels. This reinforces the role of hormonal receptors in the pathology of breast cancer, where elevated CA15.3 might indicate more aggressive or advanced disease in patients with positive ER and PR statuses.

However, Grade did not show a significant association with CA15.3 levels (Chi-squared = 0.044, p-value= 0.978), indicating that the tumour grade does not significantly influence CA15.3 levels in our study. This result suggests that CA15.3 levels might not vary considerably across different tumour grades.

Multivariable Analysis

We conducted a Multivariable Logistic Regression model to examine the influence of several factors on the likelihood of having CA15.3 levels above 30. The factor for age (>48 years) was found to be significantly associated with higher CA15.3 levels (OR: 3.27, 95% CI: 1.18 to 9.63, p-value:9.63E-06). The individuals older than 48 years are 3.27 times more likely to have CA15.3 levels above 30u/ml compared to those younger than 48 years. This highlights the increased risk of elevated tumour markers with advancing age, which is consistent with age-related changes in cancer progression. While other factors like tumour grade, Her2/neu, ER, and PR statuses showed non-significant association.

Model's Performance

The ROC curve analysis indicates that the logistic regression model demonstrates moderate ability in differentiating between various CA15.3 levels, with an Area Under the Curve (AUC) of 0.679 (95% CI: [0.6111, 0.7464] (DeLong)). This suggests that the model correctly classifies approximately 67.9% of the cases. Despite this, there is potential for improvement in the model's predictive accuracy. The statistics in Table 3 revealed that the optimal threshold for predicting elevated CA15.3 levels is 0.507. At this threshold, the model achieves a sensitivity of 0.479 and a specificity of 0.859, indicating that while it is more effective at correctly identifying cases without elevated CA15.3 levels, it may miss some cases with elevated levels. The positive predictive value (PPV) and negative predictive value (NPV) were 0.613

Table 3. Performance Metrics of Logistic Regression Model at the Optimal Threshold Using Youden Index

Metric	Value
Threshold	0.507
Sensitivity	0.479
Specificity	0.859
PPV	0.613
NPV	0.78
Accuracy	0.738
Youden Index	1.338
Precision	0.613
Recall	0.479
FDR	0.387
FPR	0.141

and 0.780, respectively, highlighting the model's moderate success in correctly predicting the presence or absence of elevated CA15.3 levels. The overall accuracy of the model is 0.738, and the Youden Index is 1.338. While the model shows some promise, it may benefit from the inclusion of additional clinical factors that could further enhance its ability to predict CA15.3 levels accurately.

Discussion

Breast cancer is among the most common malignant cancers in North East India. The correlation between breast cancer and CA15.3 involves using the CA15.3 proteins as a tumour marker. Elevated levels of CA15.3 can be associated with breast cancer, particularly in monitoring disease progression or recurrence.

Mousavi et al.2006 found that it was reported from in Iran that over 36% of breast tumours occur in women under 40 years of age[26], indicating a significant burden of breast cancer in that country. The age range of Pakistani women with breast cancer spanned from 32-75 years, with an average age of 48.3 years. Ahmed et al. [27] reported that out of 24 cases 62.5% were more than 40 years of age and 37.5% cases were below 40 years in Pakistan. In our study in bivariate chi-square test of association age was found to have a highly significant association with CA15.3 levels where p-value= 2.53E-05. This indicates that there is a strong statistical relationship between age and CA15.3 levels.

Our study also revealed that in Multivariable Logistic Regression model to examine the individuals older than 48 years are 3.27 times more likely to have CA15.3 levels above 30 compared to those younger than 48 years. This highlights the increased risk of elevated tumour markers with advancing age, which is consistent with age-related changes in cancer progression. While other factors like tumour grade, Her2/neu, ER, and PR statuses showed non-significant associations.

In breast cancer age is one of the most significant risk factor. Women over 70 years old with ductal carcinoma in situ typically receive less aggressive treatments while some studies have found no significant differences in tumour size , hormone receptor status, or other pathological features related to age. Additionally, the five-year local local recurrence rate is lower in older patients (3%) compared to women under 40 years old [28].

In a study conducted by Pike et al., [29] he found that breast cancer is rarely found in individuals under 20 and is most commonly diagnosed in women who are perimenopausal , typically before age 50.

In another study Kakugawa et al., [30] found that breast cancer may be associated with various hormonal factors based on the status of hormone receptors.

In some studies ,it was found that Serum CA15.3 levels are highly significantly associated with both ER status and HER2/neu status. ER status shows a negative correlation with CA15.3 levels, whereas Her2/neu status exhibits a positive correlation. PR status does not show a statistically significant correlation with serum CA15.3 levels. The literature presents conflicting findings, with most studies reporting no correlation between CA15.3 and various hormonal receptor statuses, while some studies do identify correlation [31-34].

In our study Her2/neu (human epidermal growth factor receptor 2 status also showed a significant association with CA15.3. This suggests that patients with positive Her2/neu status are more likely to have elevated CA15.3 levels. Her2/neu status is an important factor in breast cancer prognosis and treatment, indicating that CA15.3 levels might reflect tumour biology influenced by hormonal factors.

In some research it was found that serum levels of HER2/neu and CA15.3 can be valuable in detecting disease progression in various subgroups of women with metastatic breast cancer. The findings of this study demonstrate a significant association between elevated circulating CA15.3 levels and Her2/neu positivity. In Iraq, these results are consistent with those of a parallel study conducted by Al-Siagh and colleagues [35].

CA15.3 is a well-establised tumour marker for monitoring breast cancer patients, with a positivity rate of 51%. When combining HER2 and CA15.3 serum status, the detection rate increased to 68%. Similar findings have been reported in other studies, suggesting that measuring both serum HER2 and CA15.3 can enhance the sensitivity for early diagnosis of metastatic disease compared to using a single marker alone[36-40].

The progression of breast cancer is frequently associated with alterations in the expression of PR and Her2/neu receptor status (Liu et al.,) [41]. Serum CA15.3 levels were elevated in 39/72 ER+/PR+ cases and in 14/72 ER+/PR- cases. This indicates a strong correlation between estrogen receptor status and increased CA15.3 levels, finding consistent with Bensouda et al.,2009 [42].

In conclusion, our findings also demonstrated significant association of ER (Estrogen Receptor status) and PR (Progesterone Receptor status) with CA15.3 levels. These findings suggest that estrogen and progesterone receptor statuses are important factors influencing CA15.3 levels. This reinforces the role of hormonal receptors in the pathology of breast cancer, where elevated CA15.3 might indicate more aggressive

or advanced disease in patients with positive ER and PR statuses. This study shows that CA15.3 level in Breast cancer patients is strongly influenced by ER,PR and Her2/neu status as well as the age of the patient.

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Conflict of Interest

All the authors declare that there is no conflict of interest with regard to this study.

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