

## Recurrence of Breast Cancer Among Bangladeshi Women Using Two Serum Protein Tumor Markers, Carcinoembryonic Antigen (CEA) and Carbohydrate Antigen 15-3 (CA15-3): A Prospective Observational Study

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**ABSTRACT:** *Patients with breast cancer may develop recurrence even after adequate primary therapy. Besides clinical examination and imaging, serum protein tumor markers (SPTMs) measurements are used for follow-up. To find out the association of two postoperative SPTMs (e.g., Carcinoembryonic antigen/CEA, Carbohydrate antigen15-3/CA15-3) with the future recurrence of breast cancer among Bangladeshi women. Prospective-observational study was conducted among purposively-selected one hundred Patients (who underwent surgery before six months) during their routine follow-up visit to an oncology/surgical setting in Dhaka Medical College Hospital, Bangladesh. Postoperative CEA (cut-off:5ng/mL) and CA15-3 (30 U/mL) were measured at a single point time by 'chemiluminescent Immuno assay.' Patients were then followed up for one year to detect any recurrence. Quantitative and categorical variables were compared by Student's t-test and Fisher's exact test, respectively. Sensitivity, specificity, and AUC (Area under the curve) of both SPTMs were estimated. Most (64%) of the patients were postmenopausal (Mean-age: 49.8±12.1) with elevated CA15-3 (32%) and CEA (18%). Overall recurrence*

*was 18%, and only CA15-3 was found to be associated with visceral (hepatic and bone) recurrence (P=0.015). The sensitivity and specificity of CEA and CA15-3 were 22.22%, 82.9%, and 66.7%, 75.6%, respectively, while combined sensitivity increased by 6.25%. The AUC of the receiver operating characteristics (ROC) curves were 0.62, 0.82, and 0.88 for CEA, CA15-3, and combination, respectively. Postoperative CA15-3 has been shown to have the capacity to rule out visceral recurrence with a reasonably high probability. Since the specificity of CA15-3 is pretty good, it may detect early recurrence following primary treatment of carcinoma breast.*

**KEYWORDS:** Carcinoembryonic Antigen; Carbohydrate Antigen 15-3; Recurrence, Breast cancer; Bangladeshi women

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## INTRODUCTION

Cancer is a leading cause of death worldwide, accounting for nearly ten million deaths in 2020, and metastases are the primary cause of death from cancer [1]. Breast cancer (BC) is heterogeneous [2, 3] and remains the topmost frequent malignancy among females in the world in 2020 in terms of new cases of cancer [1]. Global cancer observatory (Globocan, 2020) also reported the same for Bangladesh (43.8% new cases and 5-year prevalence rate of BC 48.6%) [4], and mentioned that breast cancer ranked top [4,5] among the five most frequent cancer deaths in women (41.7%) in Bangladesh, while second leading causes of death reported cervical cancer [4]. Low and middle-income countries (LMICs) like Bangladesh, where health systems are overstretched and resource-poor [6-9]. Cancer survival tends to be poorer primarily because of a late-stage diagnosis and limited access to timely and standard care treatment [10], leading to higher mortality for non-Communicable diseases [4, 8, 11]. Although disease-free survival (DFS) or overall survival (OS) of breast cancer patients has improved over the past few decades owing to better diagnostic screening methods. However, 5-year DFS rates are  $\leq 50\%$  in developing/underdeveloped populations and  $>75\%$  in developed countries [10]. Breast cancer often recurs locally in the same/contralateral breast or as a distant recurrence/metastasis. About 40% of all BC patients suffer a recurrence; most die with a 5-year overall survival (OS). The risk of recurrence is highest in the first 2-3 years and then decreases continuously, although it never reaches zero [12].

Breast cancer most often involves glandular breast cells in the ducts or lobules. Most patients present with an asymptomatic mass discovered, and a biopsy confirms the diagnosis. Treatment usually includes surgical excision, often with radiation therapy, with or without adjuvant chemotherapy, hormone therapy, or both [13]. The axillary node status remains the main prognostic factor of BC patients, especially those

with early-stage disease [3]. However, recent studies document that different serum protein tumor markers (SPTMs) reportedly show combined prognostic characteristics [14-20]. Carcinoembryonic antigen (CEA) and Carbohydrate antigen15-3 (CA15-3) have been two SPTMS in the clinical fields of breast cancer for more than two decades [14, 15, 21]. These tumor markers are being used in postoperative surveillance following primary treatment and monitoring therapy in advanced diseases [15, 16, 22-24]. Their measurements are potentially more valuable for clinical practice than conventional pathologic tests like histopathology [3]. However, earlier expert panels recommended using them with diagnostic imaging, history, and physical examination [25, 26] because of their low diagnostic sensitivity for early disease [14, 15, 20, 27]. In reality, the validated result of a randomized trial for measuring postoperative serial serum protein tumor markers testing on recurrence in asymptomatic BC patients is unavailable to date [15]. Nevertheless, in recent years, many studies reported that multiple SPTMs showed increasing accuracy in detecting early breast cancer recurrences [22-24, 28-31].

Breast cancer incidence and prevalence are increasing alarmingly among both premenopausal [8, 11, 32] and menopausal women in Bangladesh [5, 33]. As mentioned above, like other low and middle-income countries (LMICs), Bangladesh is in its primitive stage of cancer prevention or control or treatment due to structural barriers. No population-based cancer registry (PBCR) exists here; lack of trained professionals or equipment, overwhelming treatment costs, and wrong diagnoses are ubiquitous [4, 6-9, 11]. Socio-economic and cultural issues like more rural patients, illiteracy, poverty, lack of knowledge/awareness on cancer, and human rights and governance issues also exacerbate the situation [5,6,8,9,32,33]. Furthermore, 90% of metastasis or late diagnosis (stage III-IV) cases further worsen the situation [5, 6, 8, 9, 11]. All breast cancer patients need an effective lifelong follow-up as recurrence may develop at any time. However, when treatment failure occurs, it lowers disease-free survival (DFS) or overall survival (OS), brings significant problems for clinicians [2, 3], and enhances enormous suffering for the patients, so detecting early relapse and reducing tumor-related symptoms and complications are urgent for BC patients. Surgical intervention is only the treatment option for BC patients in Bangladesh as breast-conserving surgery is performed less frequently [8]. Usually, bone scans, positron emission tomography-computed tomography (PET-CT), or magnetic resonance imaging (MRI) are used to detect recurrence when patients are back with symptoms [8]. Protein markers often rise in the asymptomatic patient during the follow-up period. Which are minimally invasive, cost-effective, and reflect the DFS or OS [20, 21] with a dynamic prognosis evaluation and repeatability as automated assays are available [3, 12, 15, 21]. Appropriate imaging facilities to detect early recurrence are expensive, and availability is limited in Bangladesh [6-9].

Additionally, research data on serum protein tumor markers (SPTMs) in literature are scarce in Bangladesh [8]. This follow-up study aimed to determine the association of the serum tumor markers CEA and CA15-3 with the recurrence. These two serum protein tumor markers' postoperative significance has yet to be studied. To the best of the authors' knowledge, this study is the first in Bangladesh to evaluate the prognostic significance of postoperative CEA and CA15-3 for the recurrence of BC. Thus, given the importance of earlier recurrence detection contributing to a lower mortality rate for cancer diseases [5, 6, 8, 9, 32-34], this study evaluated the recurrence pattern of carcinoma breast and aimed to discover the association of CEA and CA15-3 in the early detection of BC patients.

## **MATERIALS AND METHODS**

To find out the association of postoperative serum protein tumor markers with breast cancer recurrence, postoperative CEA and CA15-3 were estimated single-time at the baseline. The recurrence pattern was followed-up throughout the following year's period with 3-month intervals. The Research Question was if there was any association between postoperative CEA and CA15-3 with BC recurrence among Bangladeshi women.

### **Study design, subjects, place, and period**

This prospective-observational study was conducted among one hundred (n=100) female patients who attended the Surgery or Radiotherapy outpatient department in Dhaka Medical College Hospital (DMCH), Bangladesh, for clinical follow-up in the standard surgical or oncology setting during the period July 2018 to June 2019. At first, 130 patients were enrolled; however, some patients were unavailable or unresponsive at different follow-up periods (as most were from villages and poor), so incomplete data (n=30) were discarded after the follow-up period.

### **Selection of patients and ethical approval**

Patients were purposively selected according to inclusion and exclusion criteria. Inclusion criteria were female breast cancer patients who underwent mastectomy (n=96) or breast-conserving surgery (n=04) at least six months ago and completed radiotherapy/chemotherapy/or continued hormone therapy. Exclusion criteria were a history of breast cancer surgery with a positive resection margin, male breast cancer patients, and a history of incomplete treatment. Both verbal and written (signature/thumb impression) consent was taken from each patient according to the Helsinki Declaration at the beginning of the study, and patients' confidentiality was also maintained. The Ethical Clearance Committee of Dhaka Medical College Hospital approved the study in Dhaka, Bangladesh [<sup>Ref</sup>Memo No. MEU-DMC/ECC/2018/256 (R), Dated 08-11-2018].

## **Data Collection**

### ***Baseline***

Data were collected by a pretested data collection sheet containing all the variables of interest. Demographic variables (Age and Menopausal status) were documented; from each patient, 1-2 ml venous blood sample was collected in EDTA (Ethylene-diamine-tetra-acetic acid) anticoagulant tubes to examine Postoperative CEA and CA15-3 level (before the 1-year follow-up period). They were followed up for one year at 3-month intervals by history and physical examination to detect recurrence.

### ***Follow-up period***

By history and physical examination, Clinical variables (mode of breast cancer recurrence) were observed and documented during their routine "follow-up" visit to an oncology or surgical setting. Previous operation notes and histo-pathological reports were also adequately judged. If breast cancer recurrence was suspected clinically, abdominal ultrasonography, chest X-ray, isotope bone scan, or biopsy was arranged as indicated. Computerized tomography of the chest and abdomen was done in certain unequivocal hepatic and lung lesions cases. After the breast cancer recurrence was confirmed, they were categorized as visceral, bony, lymph nodal, or local recurrence.

## **Biochemical analysis**

Blood samples of breast cancer patients were centrifuged at 4000 rpm for 5 minutes to separate the serum, then transferred into Eppendorf tubes and stored at minus 80°C (-80°C) until analysis. Single-time serum CEA and CA15-3 were estimated with 'chemiluminescent Immuno assay' (CLIA) by employing 'IMMULITE 2000'. Elevated serum protein tumor markers (SPTMs) were documented if CA15-3 was  $\geq 30$  U/ml [17] and CEA  $\geq 5$  ng/ml [35]. Laboratory analysis was carried out in the biochemistry lab of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

## **Statistical Analysis**

Collected data were edited manually, rechecked data were entered into the computer, followed by proper scrutiny and cleaning. Statistical analyses were done using Microsoft Excel, 2010 (Microsoft Corporation, Washington, USA) and web-based computer software– Graph Pad Software, 2017 (Graph Pad, Inc., USA). Quantitative data were expressed as mean ( $\pm$ SD/standard deviation), compared by Student's *t*-test. Qualitative data were expressed as frequency (n) and percentage (%), compared by chi-square-test ( $\chi^2$ ) or Fisher's exact test. The sensitivity and specificity [36] of CEA and CA 15-3 were calculated to evaluate their roles as diagnostic tools for early detection of recurrence. Sensitivity was computed in relapsed patients as true positive (TP) (having elevated markers and recurrence both) divided by the total number of true relapses (TP+FN or false-negatives), i.e., Sensitivity=TP/(TP+FN). Specificity was computed as

the no recurrence in the absence of elevated marker levels (true negatives/TN) divided by the number of true negatives (TN) plus false positives (FP), Specificity=  $TN/(TN+FP)$ . A P-value of  $<0.05$  was considered to indicate statistical significance.

## RESULTS

Table-1 shows that the mean age of the patients was 49.8 ( $\pm 12.1$ , range 27–72) years. Maximum patients (46%) are 51-60 years old. Most (64%) of the patients were postmenopausal, while 36% were premenopausal. The postmenopausal group also had elevated serum markers ( $n=34$ ) than the premenopausal group ( $n=16$ ). During the follow-up period, 50% ( $n=50$ ) of the patients had normal serum protein tumor markers, while CEA and CA15-3 were elevated among the other half ( $n=50$ ).

Table-2 postulates that CEA (ng/mL) and CA15-3 (U/mL) were elevated in 18% (18/100) and 32% (32/100) study patients, respectively, and a total of 18 patients developed recurrence among elevated both tumor markers ( $n=50$ ). Recurrence was found in the form of visceral (12%), lymph node (4%), and local (2%).

Table 3 describes the sensitivity, specificity, and positive and negative predictive value of CEA and CA15-3 and their association with breast cancer (BC) relapse. Here 14 patients had normal CEA levels despite having recurrence (FN/False negative), and 04 patients (TP/True positive) had elevated CEA levels with recurrent BC. On the other hand, 12 patients with elevated CA15-3 levels developed recurrence (TP/True positive), and 06 patients (FN/False negative) had recurrence without elevation of CA15-3. The association of the elevation of serum protein tumor markers with breast cancer recurrence was significant only for CA15-3 ( $P=0.015$ ), and serum CEA showed an insignificant association ( $P=.66$ ) with breast cancer recurrence. The sensitivity and specificity of CEA and CA15-3 were 22.22%, 82.9%, and 66.7%, 75.6%, respectively, and combined sensitivity was increased by 6.25%.

Table-4 represents that CA15-3 is the most sensitive tumor marker for early detection of visceral recurrence, especially liver (sensitivity-100%) and bony recurrence (sensitivity-100%).

The Area under the curve (AUC) of the receiver operating characteristics (ROC) curve was respectively 0.82 and 0.62 for CA15.3 (figure-1,  $P<0.001$ ) and for CEA (figure-2,  $P>0.05$ ). However, ROC-combination showed (figure-3) to be increased (0.88) insignificantly ( $P>0.05$ ).

Table 1 Distribution of the study patients by age and menopausal status along with elevated serum protein tumor markers

Age (years)	patients n (%)	Menopausal status	Total N (%)	Serum protein Tumor Markers n (%)		
				Normal	Elevated	
					CEA	CA15-3
<b>Premenopausal</b>						
≤30	08 (08.0)	Pre	36	20	06	10
31 – 40	16 (16.0)	Pre	(36.0)	(40.0)	(33.33)	(31.25)
41 – 50	12 (12.0)	Pre				
<b>Postmenopausal</b>						
51 – 60	46 (46.0)	Post	64	30	12	22
61 – 70	14 (14.0)	Post	(64.0)	(60.0)	(66.67)	(68.75)
>70	04 (04.0)	Post				
<b>Total</b>			100	50	18	32
<b>Mean age ± SD</b>	<b>(49.8 ± 12.1)</b>		(100%)	(50%)	(18%)	(32%)
<b>Age Range (minimum-maximum) 27 – 72 years</b>						

Table 2 Distribution of the study patients by postoperative tumor marker's type and site of recurrence

Types of tumor markers (n=100)	Patient n (%)	Recurrence n (%)
<b>CEA (ng/mL)</b>		
< 5	82 (82)	14 (14) (False negative/FN)
≥ 5	18 (18)	04 (4) (True positive/TP)
<b>CA 15-3 (U/mL)</b>		
< 30	68 (68)	06 (6) (False negative)
≥ 30	32 (32)	12 (12)

		(True positive)
Types of Recurrence (n=18)	Sites	n (%)
Visceral recurrence (n=12)		12 (12)
	<i>Lungs</i>	04 (04)
	<i>Liver</i>	02(02)
	<i>Bone</i>	06(06)
	<i>Brain</i>	00 (00)
Lymph node recurrence (n=04)		04 (04)
Local recurrence (n=02)		02 (02)
<b>Total</b>		<b>18 (18)</b>

Table 3

Sensitivity, specificity, positive and negative predictive values of CEA and CA15-3 and association with the recurrence of breast cancer

Serum protein Tumor Markers (n=100)		Recurrence of Breast-Cancer			Estimation of the Parameters			
		Present (n=18)	Absent (n=82)	P-value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CEA (ng/mL)	Elevated ( $\geq 5$ ) (n=18)	04	14	0.66	22.2	82.9	22.2	82.9
	Normal (<5) (n=82)	14	68					
CA15-3 (U/mL)	Elevated ( $\geq 30$ ) (n=32)	12	20	0.015 <sup>a</sup>	66.7	75.6	37.5	91.2
	Normal (<30) (n=68)	06	62					
<b>Overall Recurrence</b>		<b>18%</b>						
<b>Combined CEA and CA15-3</b>					<sup>b</sup> 72.9%	66.2%	39.2%	70.2%

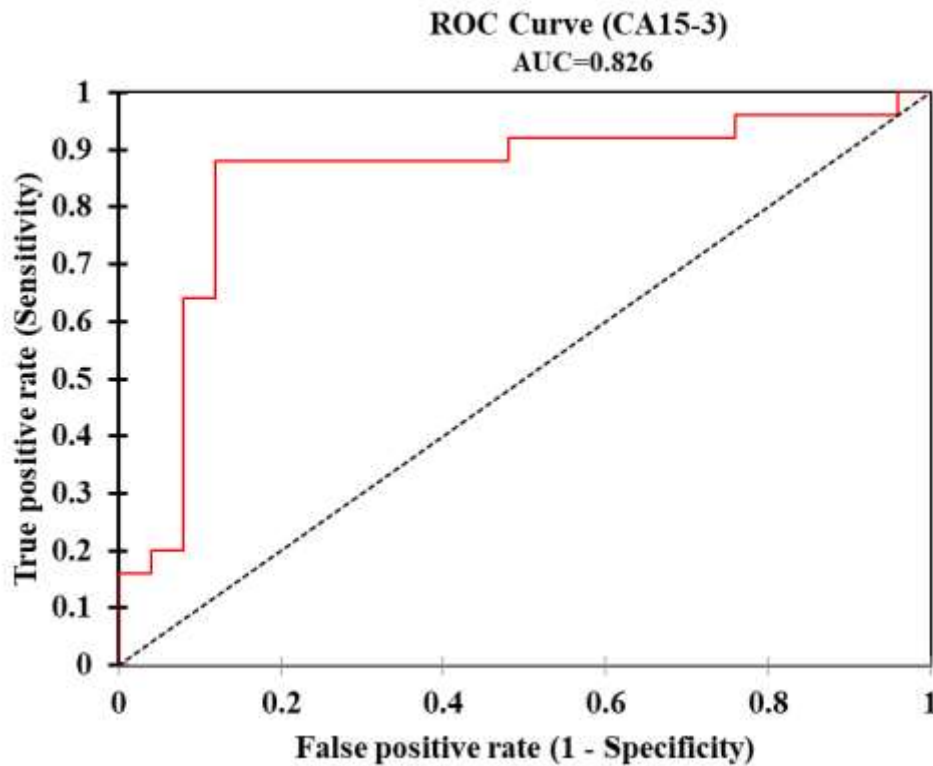
<sup>a</sup>Significant P<0.05 (Fisher's exact test), Positive predictive value=PPV, Negative predictive value=NPV

<sup>b</sup>Combined sensitivity of CEA & CA15-3 (increased by 6.2%)

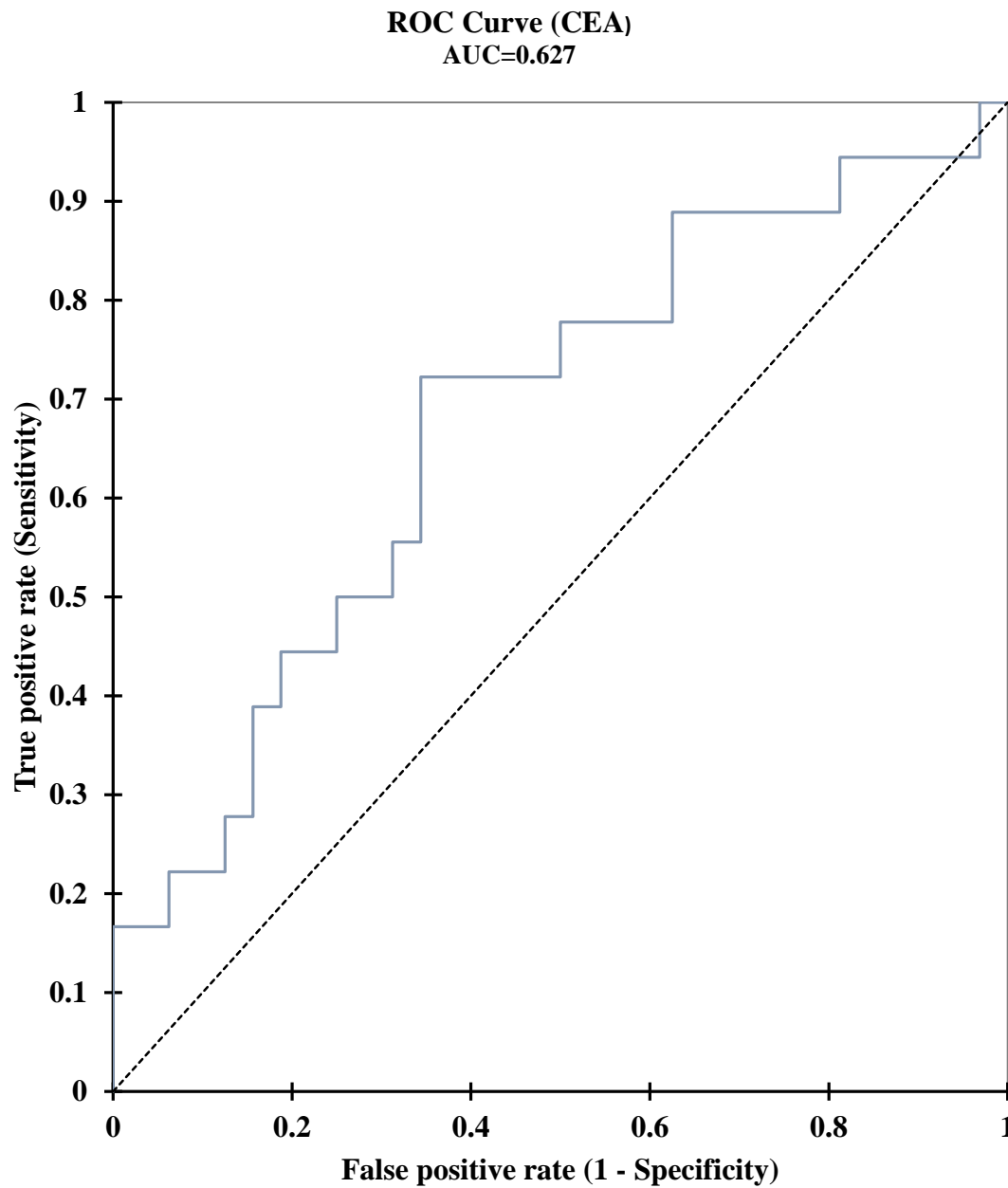


Table 4 The individual and combined sensitivity of serum CEA and CA15-3 levels by the site of recurrence (n=18)

Site of recurrence	Sensitivity		
	CEA	CA15-3	Combined CEA & CA15-3
Visceral recurrence	33.3%	83.3%	88.3%
Lungs	00.0%	50.0%	50.0%
Liver	26.0%	100.0%	100.0%
Bone	33.0%	100.0%	100.0%
Lymph-node recurrence	00.0%	50.0%	50.0%
Local recurrence	00.0%	00.0%	00.0%



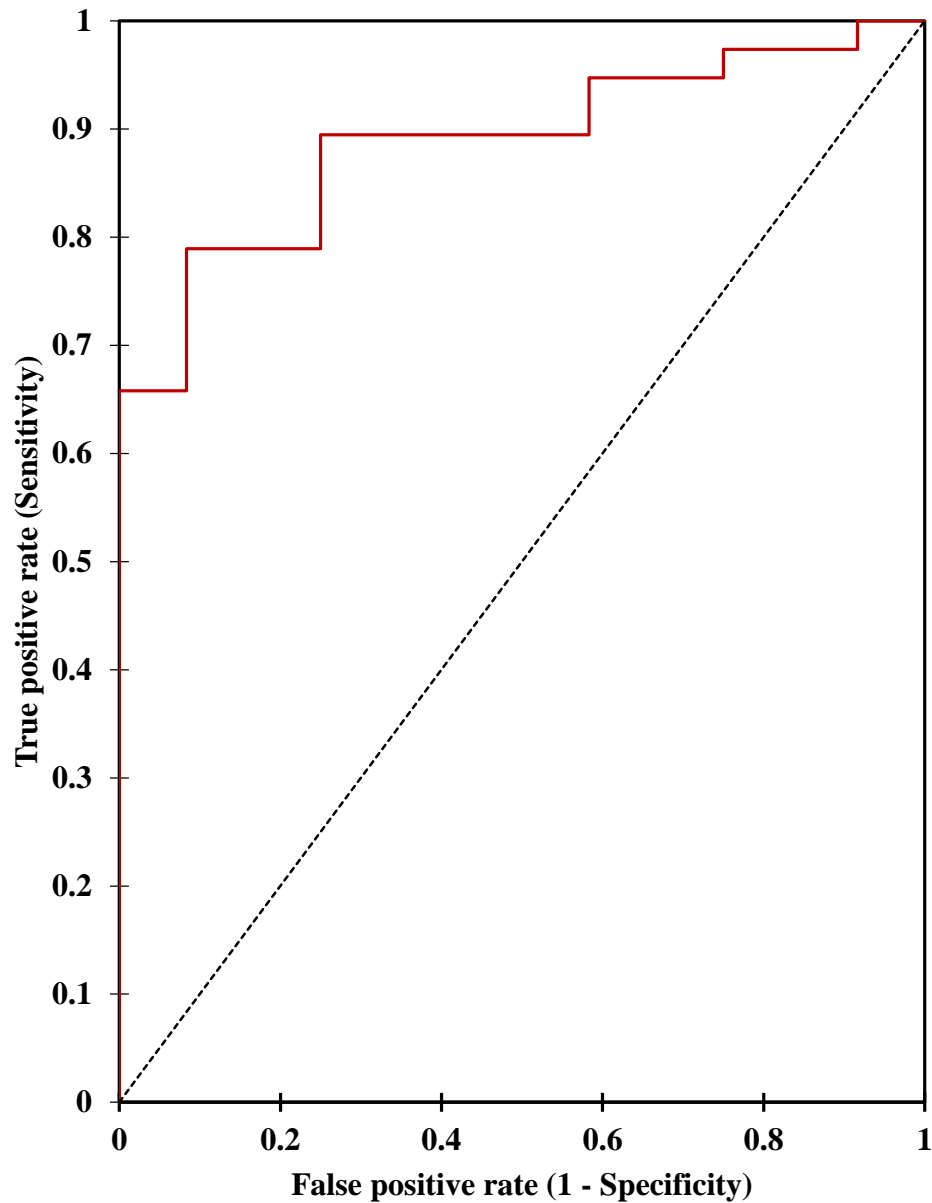
**Figure-1** Receiver operating characteristics (ROC) curve of CA15-3 with 0.826 areas under the curve (AUC)

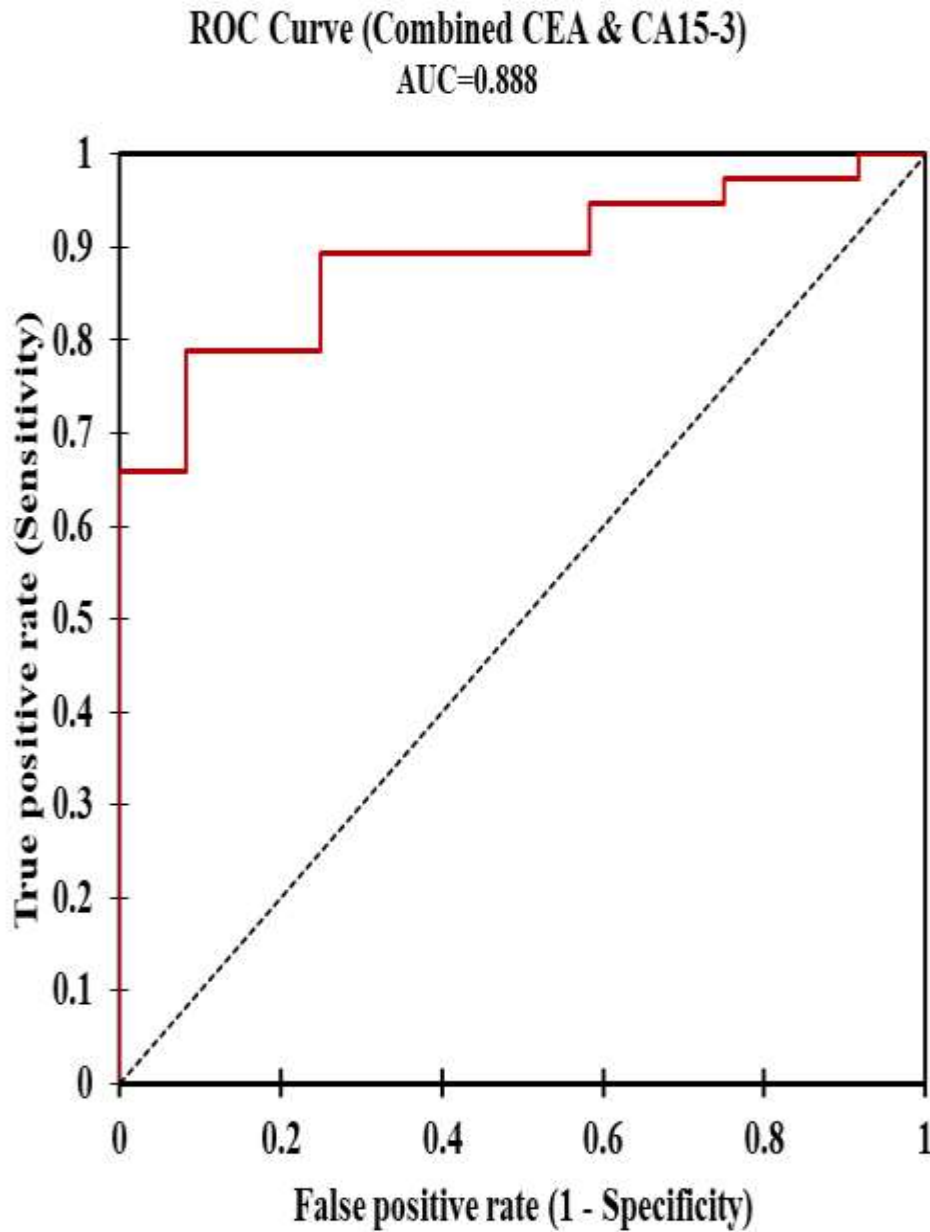


**Figure-2** Receiver operating characteristics (ROC) curve of CEA with 0.627 areas under the curve (AUC)

**ROC Curve (Combined CEA & CA15-3)**

**AUC=0.888**





**Figure-3** Receiver operating characteristics (ROC) curve for combined CA15-3 and CEA with 0.888 areas under the curve (AUC)

## DISCUSSION

Breast cancer (BC) is one of the leading causes of death among women in Bangladesh, and BC recurrences are not uncommon among them. This study explored the association of postoperative CEA and CA15-3 with the pattern of recurrence of carcinoma breast and their diagnostic role in detecting early recurrence. Most subjects (64%) of the present study were postmenopausal with a mean age of 49.8 years, who were also predominated with elevated CEA and CA15-3 levels than their premenopausal counterpart. The age limit reported by most Western studies was 58 to 62 years [23, 24 37, 38]; this may be due to geographical variation, physiology, and race. Contrarily, most of the studies in Bangladesh [8,11,32] reported that BC is predominated in premenopausal (15–44 years) women. It might be due to only one hospital-based cancer registry track (nonexistence of Population-based cancer registry or PBCR), and possibly missing cases of postmenopausal women for socio-cultural reasons [6-9]. However, this study also documents that postmenopausal BC cases are increasing like other studies [5, 33] in Bangladesh.

During one year of follow-up, two serum protein tumor markers (SPTMs) were elevated in half of the patients, and the prevalence of recurrence for elevation (true-positive) was higher in CA15-3 (12/32=37.5%) than in CEA (4/18=22.2%), which is similar to other studies [18, 19, 21, 26, 35, 38]. However, the overall recurrence of carcinoma breast was 18% higher reported than elsewhere [22-24]. Variations might be due to different cut-off values/sample sizes/test assays/or follow-up periods used in different studies. As optimal cut-off levels remain unknown [20], studies reported using short follow-up [22, 23], and the cut-off for CA15-3 (30 U/mL) [17, 35] also showed similar results in this study. In contrast, the estimation of CA15-3 with higher [18, 37] and lower cut-off [19-21, 39] than this study also reported. However, postoperative higher cut-off (>40 U/mL) was reported to be a risk factor for recurrence<sup>37</sup>, and decreased cut-offs $\geq$ 21.76 U/mL and 13.3 U/ml were documented to be correlated with bone metastases [39] and worse disease-free survival (DFS), respectively [20].

Both dissonance and agreement are available in the literature regarding the association of CEA and CA15-3 with the recurrence or metastatic breast cancer (MBC). In this study, CA15-3 was the independent prognostic factor in detecting MBC, similar to Darlix *et al.* (2016) [30]. The association of this marker with hepatic and bony recurrence agrees with other studies [19, 35, 39]. Daniele and co-workers (2013) [37] reported that postoperative elevation of CA15-3 is a significant risk factor for BC recurrence, while preoperative elevation may predict cancer progression in postoperative patients. It is due to the metastatic potentiality of CA15-3 (member of the mucin family (MUC1) as a trans-membrane glycoprotein whose cytoplasmic tail acts as a scaffold for several signaling pathways. A signaling molecule (non-receptor

kinase Src) promotes cell proliferation, migration, adhesion, and motility. Mucin one (MUC1) gene is overexpressed in malignant breast tumors and correlates with tumor mass, nodal status, presence of metastasis, and resistance to anti-hormonal therapy [40]. Contrarily, an elevation of CEA was a significant predictive factor for the recurrence of visceral/bone/multiple metastases also reported elsewhere [16, 19]. However, in recent years, the elevation of both CEA and CA15-3 was documented to be associated with the recurrence of MBC either in postoperative [16, 22-24] or preoperative [16, 20-22], or in both phases [16, 20, 22]. According to a longitudinal study, Lee and colleagues (2013) [16] reported that elevated tumor marker levels are more frequently observed in metastatic breast cancer (MBC) patients than in primary breast cancer. Patients with elevated SPTM levels before surgery also showed more frequent elevation at recurrence.

This study showed that CEA's sensitivity (and AUC of ROC) is lower than CA15-3. Combined sensitivity increased ( $P>0.05$ ) by 6.25%, which is reported similarly by Guadagni and colleagues (2001) [38] for the overall population in an earlier study. Sensitivities are difficult to compare due to methodological variations (cut-off points/test assays/different follow-up times/sample size). Only a few studies [17, 24, 28, 29, 31, 38] included combined sensitivities of CA15-3 and CEA and reported that combination enhanced sensitivities in detecting MBC (ranging from 55.8% to 95.2%). However, CEA has worse ROC in this study than CA15-3, which was reported as the opposite in a recent study [20].

## CONCLUSION

This study result shows that postoperative tumor marker CA15-3 significantly influences BC recurrence, incredibly visceral (hepatic and bone) recurrence among Bangladeshi women with a reasonably high probability. Since the specificity of CA15-3 is pretty good, it may detect early recurrence following primary treatment of carcinoma breast.

## Strengths and Limitations

Few studies in lower-middle-income countries (LMICs) focus on using tumor markers to measure breast cancer recurrence in clinically asymptomatic patients. Women in LMICs have yet to benefit from recent advances in breast cancer diagnosis, especially in Bangladesh, where cancer control is a challenging endeavor influenced by myriad forces. Cancer treatment is very costly and faces structural constraints. More importantly, knowledge and awareness level is abysmal among the general population, especially the rural population. [6] Serial measurement of postoperative serum CA15-3 can be used as a cheaper/easy-to-perform measure to detect recurrence in clinically asymptomatic patients following primary treatment of carcinoma breast. However, the present study was conducted at a brief follow-up

period with budgetary constraints, and estimation of serum protein tumor markers (SPTMs) at each follow-up interval period (after three months) was not possible to conclude about 'spike'/or 'lead time for detection of recurrence.'

### **Recommendations**

The use of postoperative CA15-3 can be recommended to detect early recurrence following primary treatment of carcinoma breast and thus restore patients' quality of life (QOL). It can also be used to plan follow-up protocol for effective management of metastases or surveillance and monitoring after primary surgery. However, to find out the optimum lead time of recurrence, [24] the cut-off value of CA15-3, and to validate this study's findings, a longitudinal study with a large cohort is warranted. [20] Moreover, a prospective randomized trial for measuring postoperative biomarkers in asymptomatic women is necessary to evaluate the potential benefit of serial SPTM testing on the patient outcome or QOL. [15]

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### **Authors' contribution**

*Study concept and acquisition of data:* Kawsar M, Hossain AZMM, and Alam ABMK

*Study supervision and suggestions:* Hossain AZMM and Alam ABMK

*Statistical analysis and interpretation:* Kawser M, Hasan M, and Kawsar M

*Drafting, manuscript preparation, and revision:* Kawser M, Hasan M, Kawsar M, Hossain AZMM, and Alam ABMK.

### **Conflict of Interests**

Authors have no conflicts of interest to declare

### **Data availability**

Data supporting these findings are available within the article or upon request.

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