Relationship Between Levels of Carcinoembryonic Antigen and Cancer Antigen 15-3 and Clinicopathological Parameters and Response to Neoadjuvant Chemotherapy in Breast Cancer

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Abstract:

Background and aim of the work: Serum tumor markers; carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) are widely used in clinical practice for detecting recurrences or monitoring treatment efficacy for metastatic breast cancer patients. We aimed to explore the relationship between serum levels of CEA, CA 15-3 before neoadjuvant treatment and clinicopathological parameters in breast cancer patients, as well as the predictive value of these two serum biomarkers in relation to response to neoadjuvant chemotherapy.

Methods: This prospective study was conducted at Helwan University Hospitals from October 2022 to September 2023. It included 50 breast cancer patients who received neoadjuvant chemotherapy.

Results: Higher T status, higher LN status and higher stage were significantly associated with higher CEA, CA 15-3 levels. While there was no statistically significant correlation between the level of CEA, CA 15-3 and molecular type or histopathological type. There was no statistical difference in serum levels of CEA and CA 15-3 between patients with partial and patients with complete response.

Conclusion: Pretreatment serum levels of CEA and CA15-3 were elevated in the majority of breast cancer patients. Higher T status, higher LN status and higher stage were significantly associated with higher CEA & CA 15-3 levels which can be related to prognosis. CEA and CA 15-3 had no significant association with molecular subtypes or response to neoadjuvant chemotherapy.

Keywords: Breast cancer, Carcinoembryonic Antigen, Cancer Antigen 15-3, Neoadjuvant chemotherapy.

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Introduction:

Breast cancer is currently one of the most commonly diagnosed cancers and the leading cause of cancer-related deaths among females, with an estimated 2.3 million new cases worldwide, according to GLOBOCAN 2022 data. In Egypt, it represents 33% of all malignancies in women. More than 22,000 new cases are diagnosed annually [1].

Serum tumor markers can be easily detected, and they play an important role in many malignant tumors, but their role in breast cancer remains controversial. There is some correlation between tumor markers and tumor clinicopathology [2].

There is some correlation between tumor markers and tumor clinicopathology. When the acquisition of tissue specimens is not available, in some cases, these

markers may offer useful information about the phenotype of the breast cancer at an early stage [3]

Of all serum tumour markers for breast cancer, CA 15-3 and CEA were most used and recommended [4-7]. The European Group on Tumour Markers recommended that CEA and CA15-3 levels should be used for prognosis assessment, early detection of disease progression and monitoring of breast cancer treatment [8].

Cancer antigen 15-3 (CA15-3) and carcinoembryonic antigen (CEA) are the mostly and recommended used markers among alotof biomarkers include also cancer antigen 27.29 (CA27.29), tissue polypeptide antigen (TPA), circulating extracellular domain of HER-2, and tissue polypeptide-specific antigen (TPS).[9]

CA15-3 is a serum tumor marker for BC extensively used in clinical practice. CA15-3 is non-invasive, easily available, and a cost-effective tumor marker for immediate diagnosis, monitoring, and prediction of BC in early, advanced, and metastatic BC [10].

In numerous studies, elevated CA15-3 level was associated with prognosis of breast cancer with various ranges and situations. In patients with metastatic breast cancer, elevated CA15-3 level showed poor overall survival (OS) with cut-off values ranging from 20.1 to 40 U/mL. [11, 12]

Although tumor markers alone are insufficient to evaluate therapeutic response, several studies suggest that tumor marker levels correlate with treatment response [13, 14]

Detection of serum tumor marker as easily accessible and soluble circulating markers in females with breast cancer is a useful strategy for evaluation of prognosis and selection the type of treatment.

While some authors suggested routine testing of tumour markers, the systematic use of serum markers in the strategies of women follow-up after breast cancer treatment is excluded from international main guidelines [15]

We hypothesized that an elevation of CEA and CA15-3 levels in patients with breast cancer could be associated with clinicopathological parameters and might be of value to assess the therapeutic response in those patients

With the great controversies in the monitoring, treatment and prognosis of women with breast cancer, hence we aimed to explore the association of serum levels of CEA and CA 15-3 preneoadjuvant treatment and clinicopathological parameters. Also, aimed to assess their relation to therapeutic response.

Patients and Methods:

Patients:

This prospective study was conducted at clinical oncology department, Helwan university hospitals. During the period from October 2022 to September 2023. Approval was obtained from Helwan University Institutional Review Board (ethical approval no: 63-2022). Consent was obtained from all patients participating in the study. The Declaration of Helsinki, the international Medical Association's guideline of ethics for studies involving humans, was followed in the conduct of this study.

The inclusion criteria were:

1- Female patients
2- Age: 18-75 years
3- Pathologically proven invasive breast cancer
4- Patients planned for neoadjuvant chemotherapy
5- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 [8].

The exclusion criteria were:

1- Male breast cancer patients
2- Metastatic breast cancer
3- Carcinoma in situ
4- Underlying serious medical condition hindering the possibility of neoadjuvant chemotherapy

Before starting neoadjuvant chemotherapy all patients were subjected to:

1- Full history taking, physical examination,
2- Laboratory investigations included (complete blood picture, liver functions test including alanine aminotransferase, aspartate aminotransferase, albumin, bilirubin, renal functions test including blood urea and serum creatinine),
3- Echocardiogram,
4- Bilateral sonomammography, computed tomography chest, abdomen, and pelvis with contrast, bone scan,

Detection of CEA and CA15-3

The commercially available CanAg CA15-3 and CanAg CEA EIA kits (FUJIREBIO Diagnostics, Inc.) are used for the quantitative determination of the cancer associated antigens in serum. The markers (CEA and CA15-3) were analyzed by direct sandwich technique by two monoclonal antibodies. When the reaction was terminated by a stop solution (0.12 M hydrochloric acid), the absorbance (optical density at 405-630nm) was measured by ELISA reader. The standard curve was prepared based on absorbance.

The concentration of serum CA 15-3 and CEA levels were measured using chemiluminescent enzyme immunoassays (ADVIA Centaur; Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA). The upper limits of normal for CA 15-3 and CEA were 31.3 U/ml and 5 ng/ml, respectively.

Serum CEA and CA 15-3 were measured one week before treatment, cutoff value of 5ng/mL was used for CEA [16]. A cutoff value of 30U/ml was used for CA 15-3 [17], these cutoff values are based on previous similar studies as they are upper limit of normal, immunohistochemistry (IHC) method was used to detect the expression of ER, PR, HER-2, and Ki-67. ER-positive and PR-positive were defined as the presence of 1% nuclear-stained cells. HER2-positivity was indicated by a 3+ or 2+ score from the immunohistochemical evaluation, and was confirmed using a fluorescence in situ hybridization (FISH) test for HER2. A cut-off point of 14% was used for Ki-67 staining. [17]

The patients were classified into four molecular subtypes, as follows: [17]

1. Luminal A: estrogen receptor (ER)-positive (ER+) and/or progesterone receptor (PR)-positive (PR+), human epidermal growth factor receptor 2 (HER2)-negative (HER2−) and low Ki67 level (< 14.0%);
2. Luminal B: ER+ and/or PR+, HER2−, Ki67 ≥ 14.0%, or ER+ and/or PR+, HER2+, Ki67 any
3. HER2+; (ER- and PR-, HER2+)
4. Triple-negative breast cancer (TNBC): ER−, PR−, and HER2−

ECOG Performance Status Scale [18]

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

A standardized neoadjuvant chemotherapy protocol was given to all enrolled patients:

All patients were treated with 4 cycles of AC (Doxorubicin 60 mg/m2 and Cyclophosphamide 600 mg/m2 at day one and repeated every 21 days). Followed by; Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 weeks, Her 2 positive patients received trastuzumab + pertuzumab along with paclitaxel.

Assessment of response to treatment

For the study, clinical tumour response and imaging response (RECIST) [19] assessed by the oncologists and available in the patients' files were used and compared with the results of tumour marker assays.

Tumour response was considered as good in patients with complete or partial remission and poor when the patient was in stabilization or progression.

pathologic response to neoadjuvant chemotherapy was defined as:

- Complete pathologic response (PCR): ypT0/Tis, ypN0,
- Non pathologic complete response (Non PCR): presence of viable tumor cells.

Statistical analysis

The collected data was revised, coded, tabulated using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). The collected data was revised, coded, tabulated using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Shapiro test was done to test the normality of data distribution. Mean, Standard deviation (± SD) were used for parametric numerical data, while Median and range were used for non-parametric numerical data. Frequency and percentage were used for non-numerical data.

Student T Test was used to assess the statistical significance of the difference between two study group means. For the comparison of more than two groups' means, one way analysis of variance (ANOVA) was used. Mann Whitney Test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups. The Kruskal-Wallis test was used to assess the statistical significance of the difference between more than two study group non parametric variables. Chi-Square test was used to examine the relationship between two qualitative variables. ROC curve analysis was performed to assess the sensitivity and specificity o CA and CEA in prediction of response. P value was set at <0.05 for significant results & <0.001 for high significant result.

Results:

This study included 50 females diagnosed with breast cancer; their mean age was 44.5±9.6 years. 12% of females were <35 years and 88% were >35 years. 38% of patients were postmenopausal and 62% were premenopausal. 50% of tumors are left sided and 50% are right sided as shown in table 1. 34% of cases had complete response to treatment and 66% had partial response. The mean CEA was 10.9±6.7, 32% of cases had normal level and 68% had elevated level. The mean CA 15-3 was 35.1±14.5, 34% of cases had normal level and 66% had elevated level as shown in table 2.

There was no statistically significant correlation between the level of CEA and patients' age, menopausal status, tumor sidedness or type of surgery as shown in table 3. Also, table 4 revealed that there was no statistically significant correlation between the level of CA 15-3 and patients' age, menopausal status, tumor sidedness or type of surgery.

Higher T status, higher LN status and higher stage were significantly associated with higher CEA levels. While there was no statistically significant correlation between the level of CEA and molecular type or histopathological type as shown in table 5.

Higher T status, higher LN status and higher stage were significantly associated with higher CA 15-3 levels. While there was no statistically significant correlation between the level of CA 15-3 and molecular type or histopathological type as shown in table 6.

There was statistical difference between patients with partial and patients with complete response regarding molecular type. Partial response group had higher frequencies of luminal B (60.6%), followed by liminal A (24.2%), while complete response group had higher frequencies of HER2 (35.3%), Triple –ve (35.3%). While, there was no statistical difference between patients with partial and patients with complete

response regarding any of pathological parameters as shown in table 7.

There was no statistical difference between patients with partial and patients with complete response regarding CEA as shown in table 8. There was no statistical difference between patients with partial and patients with complete response regarding CA 15-3 as shown in table 9.

CEA and CA 15-3 could not significantly predict response to treatment of breast cancer in the studied group (AUC= 0.576 & 0.558, respectively), p=0.384 and 0.506, respectively as shown in figure 1.

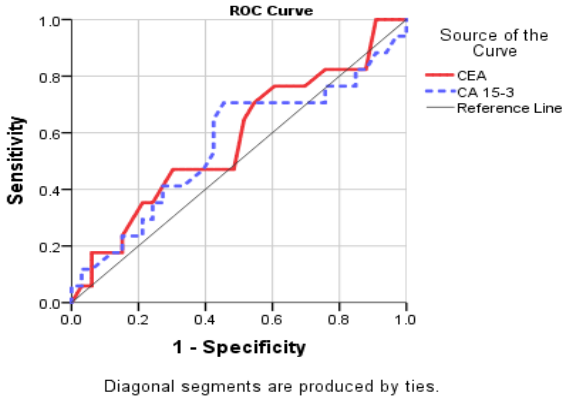

Figure 1: ROC curve of performance of CEA and CA 15-3 to predict response to treatment of breast cancer in the studied group

Table 1: Clinical criteria of the studied group

		N=50	%
Age (years)	Mean±SD	44.5±9.6	
	Range	25-70	
	≤35 years	6	12.0%
	>35 years	44	88.0%
Menopausal	Post	19	38.0%
	Pre	31	62.0%
Site	Left	25	50.0%
	Right	25	50.0%

Table 2: Pretreatment CEA and CA 15-3 in the studied group

		N	%
CEA	Mean±SD	10.9±6.7	
	Range	2-23	
	Normal level	16	32.0%
	Elevated	34	68.0%
CA 15-3	Mean±SD	35.1±14.5	
	Range	11-65	
	Normal level	17	34.0%
	Elevated	33	66.0%

CEA: Carcinoembryonic Antigen CA 15-3: Cancer Antigen 15-3

Table 3: Pretreatment CEA in relation to clinical criteria in the studied group

		CEA		Test	P value
		Mean±SD	Range		
Age	<35 years	9.83±3.43	5-13	U=0.74	0.720
	>35 years	11.15±7.01	2-23		
Menopausal	post	11.02±7.72	2-23	U=0.2	0.84
	pre	10.97±6.07	2.5-20		
Site	Left	9.72±6.58	2-20	U=1.2	0.22
	Right	12.26±6.65	2-23		
Type Surgery	BCS+ALND	10.39±5.6	2-20	K=2.4	0.29
	Lt MRM	9.13±7.08	2.1-20		
	Rt MRM	13.11±6.97	2-23		

CEA: Carcinoembryonic Antigen P > 0.05: Non significant
BCS+ALND: Breast conserving surgery + Axillary lymph node dissection
Lt MRM: Left Modified Radical Mastectomy
Rt MRM: Right Modified Radical Mastectomy

Table 4: Pretreatment CA 15-3 in relation to clinical criteria in the studied group

		CA 15-3		Test	P value
		Mean±SD	Range		
Age	<35 years	34.3±6.3	25-44	U=0.2	0.970
	>35 years	35.1±15.3	11-65		
Menopausal	Post	36.1±18.3	11.6-65	U=0.29	0.77
	Pre	34.4±11.8	11-60		
Site	Left	33.8±14.5	11-65	U=1.1	0.23
	Right	36.3±14.6	13-62		
Type of Surgery	BCS+ALND	34.1±12.4	13-60	U=0.37	0.71
	Lt MRM	32.2±15.9	11-65		
	Rt MRM	38.1±15.2	15-62		

CA 15-3: Cancer Antigen 15-3 P > 0.05: Non significant
BCS+ALND: Breast conserving surgery + Axillary lymph node dissection
Lt MRM: Left Modified Radical Mastectomy
Rt MRM: Right Modified Radical Mastectomy

Table 5: Pretreatment CEA in relation to pathological parameters in the studied group

		CEA		Test	P value
		Mean±SD	Range		
T status	cT1	2.53±0.92	2-3.6	K=34.2	<0.001*
	cT2	6.36±4.35	2.1-15		
	cT3	11.07±4.43	3-20		
	cT4	19±2.18	15-23		
LN status	N0	6.75±6.1	2-18	K=12.2	0.007*
	N1	9.8±6.19	2-23		
	N2	16±3.61	12-21		
	N3	15.52±7.33	2.1-22		
Stage	I	2.00	N/A	K=30.2	<0.001*
	II	4.6±2.38	2-12		
	III	15.34±4.75	2.1-23		
Biologic type	HER2 enriched	12.4±6.89	2.7-20	K=1.73	0.63
	Luminal A	11.45±6.73	4-21		
	Luminal B	11.32±6.98	2-23		
	Triple -ve	8.37±6.52	2-20		
Histopathological subtype	IDC G2	11.43±6.5	2-23	K=3.1	0.35
	IDC G3	9.39±7.95	2-20		
	Mucinous	13	N/A		

CEA: Carcinoembryonic Antigen
T: Tumor size
LN: Lymph node
HER2: Human epidermal growth factor receptor 2
IDC G2: Invasive ductal carcinoma grade 2
IDC G3: Invasive ductal carcinoma grade 3
P < 0.001*: high significant, P > 0.05: Non significant , P < 0.05: Significant

Table 6: Pretreatment CA 15-3 in relation to pathological parameters in the studied group

		CA 15-3		Test	P value
		Mean±SD	Range		
T status	cT1	17±1.7	16-19	K=37.1	<0.001*
	cT2	24.4±7.8	11-35		
	cT3	36±7.1	16-45		
	cT4	52.4±9.5	35-65		
LN status	N0	34.9±11.7	11-45	K=9.1	0.027*
	N1	33.8±12.2	13-60		
	N2	43.8±14.1	31-62		
	N3	44.1±18.1	11.6-65		
Stage	I	16	N/A	K=26.4	<0.001*
	II	23.3±7.6	11-36		
	III	43.1±12.2	11.6-65		
Biologic type	Her2 enriched	44.9±15.9	23-65	K=5.9	0.11
	Luminal A	36.3±12	18-59		
	Luminal B	33.8±14.6	11-62		
	Triple -ve	26.1±11.3	13-45		
Histopathological subtype	IDC G2	35.9±14.3	11-65	K=3.4	0.32
	IDC G3	37.3±15.6	16-60		
	Mucinous	31	N/A		

CA 15-3: Cancer Antigen 15-3
T: Tumor size
LN: Lymph node
HER2: : Human epidermal growth factor receptor 2
IDC G2: : Invasive ductal carcinoma grade 2
IDC G3 : Invasive ductal carcinoma grade 3
P < 0.001*: high significant, P > 0.05: Non significant , P < 0.05: Significant

Table 7: Pathological parameters in relation to response to treatment in the studied group

		Response				test	P value
		Partial		Complete			
		N=33	%	N=17	%		
T status	cT1	1	3.0%	2	11.8%	X2=1.7	0.64
	cT2	13	39.4%	6	35.3%		
	cT3	9	27.3%	5	29.4%		
	cT4	10	30.3%	4	23.5%		
LN status	N0	7	21.2%	3	17.6%	X2=3.7	0.29
	N1	18	54.5%	7	41.2%		
	N2	4	12.1%	5	29.4%		
	N3	4	12.1%	2	11.8%		
Stage	I	0	0.0%	1	5.9%	X2=2.2	0.32
	II	12	36.4%	7	41.2%		
	III	21	63.6%	9	52.9%		
Biologic type	Her2 enriched	3	9.1%	6	35.3%	X2=15.7	<0.001*
	Luminal A	8	24.2%	1	5.9%		
	Luminal B	20	60.6%	4	23.5%		
	Triple -ve	2	6.1%	6	35.3%		
Histopathological subtype	IDC G2	30	90.9%	12	70.6%	X2=5.8	0.12
	IDC G3	2	6.1%	5	29.4%		
	Mucinous	1	3.0%	0	0.0%		

T: Tumor size
LN: Lymph node
IDC G2: Invasive ductal carcinoma grade 2
IDC G3: Invasive ductal carcinoma grade 3
P < 0.001*: high significant, P > 0.05: Non significant , P < 0.05: Significant

Table 8: Pretreatment CEA in relation to response to treatment in the studied group

		Response				test	P value
		Partial		Complete			
		N=33	%	N=17	%		
CEA	Mean±SD	11.5±6.7		9.9±6.7		U=0.87	0.37
	Median	12		12			
	Range	2-23		2-20			
	Normal	10	30.3%	6	35.3%	X2=0.13	0.72
	Elevated	23	69.7%	11	64.7%		

CEA: Carcinoembryonic Antigen
P > 0.05: Non significant

Table 9: Pretreatment CA 15-3 in relation to response to treatment in the studied group

		Response				test	P value
		Partial		Complete			
		N=33	%	N=17	%		
CA15-3	Mean±SD	35.5±13.7		34.1±16.2		U=0.66	0.50
	Median	36		33			
	Range	11.6-62		11-65			
	Normal	10	30.3%	7	41.2%	X2=0.59	0.44
	Elevated	23	69.7%	10	58.8%		

CA 15-3: Cancer Antigen 15-3 P > 0.05: Non significant

Discussion:

Our objective was to investigate the association of carcinoembryonic antigen and cancer antigen 15-3 with clinicopathological parameters and their relation to neoadjuvant chemotherapy response in patients with breast cancer

We found that there was no statistically significant correlation between the level of CEA or CA 15-3 and patients' age, menopausal status, tumor sidedness or type of surgery. On the other hand, our data revealed that higher CEA and CA 15-3 levels were significantly associated with higher T status, LN status and higher stage.

These findings were in line with those of Mudduwa et al. [20], who found that elevated pre-surgical CA 15-3 level was significantly associated with larger tumor size (T1 20.0%, T2 34.8%, and T3 48.5%). Although the prevalence of high CA 15-3 level increased with TNM stage (stages I: 22.7%, II: 31.2%, and III: 42.6%), this relationship did not achieve statistical significance ($p>0.05$). This result was in contrast to our study probably because most patients in that study had a lower stage of the disease.

Similar to this, Shao et al. [21] and Lee et al. [22] found in their studies that elevated serum levels of CA15-3 and CEA prior to surgery were significantly associated with larger tumor size, axillary node metastasis, and advanced stage. This similarity can be attributed to increased tumor burden, which leads to increased serum levels of CEA and CA 15-3.

We did not observe any significant correlation between CA 15-3 and CEA values with the molecular type or histopathological subtypes of the treated patients. Likewise, [23] did not find any difference of these parameters according to immunohistochemistry assessment. Likewise, Lian et al. [2] and Mudduwa et al. [20], reported that there was no any significant association between pre-surgical CA 15-3 and CEA values and the post-treatment overexpression of ER, PR, and HER2. This similarity can be attributed to comparable patients' characteristics.

On the contrary, previous reports revealed that CA15-3 levels differ considerably based on molecular subtype [23; 24] Furthermore, Al Saihati et al. [25] reported that CEA levels were substantially higher in patients with Luminal B and HER2 positive tumors ($p=0.03$) than in patients with Luminal A and triple-negative tumours ($p=0.03$), and that CA 15-3 levels were substantially higher in patients with HER2 positive and triple-negative tumours ($p=0.02$) than in patients with Luminal A and Luminal B malignancies ($p=0.02$). This difference can be attributed to smaller sample size in that study and different patients' characteristics.

The CEA and CA 15-3 levels did not differ substantially among patients with partial and those with complete response ($P>0.05$ for both).

These results were in agreement with Wang et al. [26], who reported that pretreatment CA 15-3 demonstrated low level predictive value of response to neoadjuvant chemotherapy, and that no significant differences in carcinoembryonic antigen (CEA) serum levels were observed between the pCR and non-pCR groups. This similarity can be related to comparable patients' characteristics and same chemotherapy protocol used.

However, in the study by Al-Azawi et al. [27], patients with high concentrations of CA 15-3 before primary chemotherapy treatment had a poor clinical and pathological response, and concluded that Elevated CA 15-3 level is predictive of a poor response to chemotherapy.

Importantly, we observed that CEA and CA 15-3 could not significantly predict response to treatment based on ROC curve analysis (AUC= 0.576 & 0.558, respectively).

The lack of sensitivity and specificity of CEA led the expert groups to not recommend its measurement in the screening and diagnosis of carcinomas of various locations. Many authors highlighted the correlation between the evolving profile of CA 15-3 and the response to treatment, and various recommendations stipulate that an initial elevation of CA 15-3 which does not return to the normal reflects a lack of response to treatment and constitutes an important unfavourable prognosis factor [28].

Even in the initial assessment, the value of its measurement remains debated at the international level and some experts do not recommend it because it does not modify the therapeutic attitude [29].

Finally, no sufficient evidence was found in our study to indicate that serum tumor biomarkers (CEA and CA 15–3) should be routinely used to monitor the response to preoperative systemic treatment in breast cancer patients.

The prognostic value of CA15-3 had been proven by some studies [7,30], while other studies reported negative results [31].

CEA is less widely studied as a prognostic factor than CA15-3 because it is less positive and more controversial. Some studies reported that CEA does not allow to distinguish primary from metastatic breast cancer [32,33], but others reported that high CEA levels were associated with a poor prognosis of breast cancer [4,5,34]. These conflicting results of CA15-3 and CEA in breast cancer with respect to their prognostic value may be due to small sample sizes, variable study designs or other biases in each study.

Without more potent serum markers, although imperfect, CA15-3 and CEA remain the most commonly used biomarkers in breast cancer and are recommended for practical use by the American Society of Clinical Oncology (ASCO) [35]. Likewise, the European Group on Tumour Markers recommended the use of CA15-3 and CEA to assess the prognosis of breast cancer [36].

Study limitation

The main limitations encountered are: First small sample size and single institute study which does not allow the conclusions to be generalized to the whole population of patients treated for breast cancer. Second the advanced age of most recruited patients.

Conclusion:

Pretreatment serum levels of CEA and CA15-3 were elevated in the majority of breast cancer patients. Higher T status, higher LN status and higher stage were significantly associated with higher CEA & CA15-3 levels which can be related to prognosis. CEA and CA15-3 had no significant association with molecular subtypes or response to neoadjuvant chemotherapy.

References:

1- Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024 May-Jun;74(3):229-263.

2- Li Y, Yang D, Yin X, et al. Clinicopathological characteristics and breast cancer–specific survival of patients with single hormone receptor–positive breast cancer. JAMA Netw Open. 2020 Jan 3;3(1):e1918160.

3. Li J, Liu L, Feng Z, et al. Tumor markers CA15-3, CA125, CEA and breast cancer survival by molecular subtype: A cohort study. Breast Cancer. 2020 Jul;27(4):621-630.

4. Mohammed FZ, Gamal L, Mosa MF, et al. Assessment of CEA and CA15-3 as Potential Prognostic Markers for Breast Cancer in Egyptian Females. Alfarama Journal of Basic and Applied Sciences 2021; 2(1):44-50.

5. Imran AH, Al-atrachji SA, Al-mosawi KK (2021). Clinical important of E-Cadherin, CA15-3 and CEA in Diagnostic and Flow Up for Breast Cancer Patients. Indian Journal of Forensic Medicine and Toxicology 2021; 15(2): 4409-4414..

6. Khushk M, Khan A, Rehman A, et al. The Role of Tumor Markers: Carcinoembryonic Antigen and Cancer Antigen 15-3 in Patients With Breast Cancer. Cureus. 2021 Jul 10;13(7):e16298.

7. Uygur MM, Gümü M. The utility of serum tumor markers CEA and CA 15-3 for breast cancer prognosis and their association with clinicopathological parameters. Cancer Treat Res Commun. 2021;28:100402.

8. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019 Aug 1;30(8):1194-1220.

9- Lian M, Zhang C, Zhang D, et al. The association of five preoperative serum tumor markers and pathological features in patients with breast cancer. J Clin Lab Anal. 2019;33(5): e22875.

10. Abed SN, Mahdi HS, Sahib AS, et al. Serum Levels of Cancer Antigen 15.3 and Estrogen in a Samples of Iraqi Women with Breast Cancer Treated with Anastrazole. International Journal of Pharmaceutical Research 2020; 1:1604-1608

11. Darlix A, Lamy PJ, Lopez-Crapez E, et al. Serum HER2 extra-cellular domain, S100ß and CA 15-3 levels are independent prognostic factors in metastatic breast cancer patients. BMC Cancer. 2016;16:428.

12.Lee JS, Park S, Park JM, et al. Elevated levels of preoperative CA 15-3 and CEA serum levels have independently poor prognostic significance in breast cancer. Ann Oncol. 2013;24:1225–1231.

13. Nam S, Lim W, Jeong J, et al. The prognostic significance of preoperative tumor marker (CEA, CA15-3) elevation in breast cancer patients: data from the Korean Breast Cancer Society Registry. Breast Cancer Res Treat. 2019; 177: 669–678.

14. Khushk M, Khan A, Rehman A, et al. “The role of tumor markers: carcinoembryonic antigen and cancer antigen 15-3 in patients with breast cancer”, Cureus. 2021; (13) : 7.

15. Moschetti I, Cinquini M, Lambertini M, et al. Follow-up strategies for women treated for early breast cancer. Cochrane Database Syst Rev. 2016 May 27;2016(5):CD001768.

16- Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6): 649–656.

17- Duffy MJ, Duggan C, Keane R, et al. High preoperative CA 15-3 concentrations predict adverse outcome in node-negative and node-positive breast cancer: study of 600 patients with histologically confirmed breast cancer. Clin Chem. 2004;50(3): 559–563.

18- Zhao L, Lee VH, Ng MK, et al. Molecular subtyping of cancer: current status and moving toward clinical applications. Brief Bioinform. 2019;20(2): 572-584.

19. Dubreuil J, Cachin F, Berriolo-Ridinger A, et al. Critères d'interprétation en imagerie cancérologique solide: RECIST, PERCIST…. Médecine Nucléaire 2017; 41(3):241-248

20- Mudduwa LK, Wijayaratne GB, Peiris HH, et al. Elevated pre-surgical CA15-3: does it predict the short-term disease-free survival of breast cancer patients without distant metastasis? Int J Womens Dermatol. 2018;329–335.

21- Shao Y, Sun X, He Y, et al. Elevated levels of serum tumor markers CEA and CA15-3 are prognostic parameters for different molecular subtypes of breast cancer. PloS One. 2015;10(7), e0133830.

22- Lee JS, Park S, Park JM, et al. Elevated levels of preoperative CA 15-3 and CEA serum levels have independently poor prognostic significance in breast cancer. Ann Oncol. Elsevier. 2013; 24(5): 1225–1231.

23. Li J, Liu L, Feng Z, et al. Tumor markers CA15-3, CA125, CEA and breast cancer survival by molecular subtype: A cohort study. Breast Cancer. 2020 Jul;27(4):621-630.

24. Ruswendro D, Syamsu SA, Thabry R, et al. Association between molecular subtype of local advanced breast cancer with Ca 15-3 level. Breast Dis. 2021;40(S1):S119-S122

25- Al Saihati HA. Elevated CEA and CA15-3 Serum Levels in Different Molecular Subtypes of Breast Cancer Have Prognostic Significance. Bahrain Med Bulletin. 2023; 45(1).

26- Wang YJ, Huang XY, Mo M, et al. Serum tumor marker levels might have little significance in evaluating neoadjuvant treatment response in locally advanced breast cancer. Asian Pac J Cancer Prev. 2015;16(11);4603-4608.

27- Al-Azawi D, Kelly G, Myers E, et al. CA 15-3 is predictive of response and disease recurrence following treatment in locally advanced breast cancer. BMC cancer. 2006; 6(1):1-7.

28. Bushi S, Trebicka A. The Role of Tumor Markers for Evaluation the Course of Chemotherapy. ARC Journal of Cancer Science 2021; 7(1):01-05

29. Ruswendro D, Syamsu SA, Thabry R, et al. Association between molecular subtype of local advanced breast cancer with Ca 15-3 level. Breast Dis. 2021;40(S1):S119-S122.

30. Gonssaud B, Goussot V, Berriolo-Riedinger A, et al. Clinical value of CA 15-3 for detection of distant metastases in newly diagnosed breast cancer. Ann Biol Clin (Paris). 2017 Aug 1;75(4):421-429.

32. Ebeling FG, Stieber P. Untch M, et al. Serum CEA and CA 15-3 as prognostic factors in primary breast cancer. Br J Cancer. 2002 Apr 22;86(8):1217-22.

33. Molina R, Auge JM, Farrus B, et al. Prospective Evaluation of Carcinoembryonic Antigen (CEA) and Carbohydrate Antigen 15.3 (CA 15.3) in Patients with Primary Locoregional Breast Cancer. Clin Chem. 2010 Jul;56(7):1148-57.

34. Nan J, Li J, Li X, et al. Preoperative Serum Carcinoembryonic Antigen as a Marker for Predicting the Outcome of Three Cancers. Biomark Cancer. 2017 Feb 16;9:1-7.

35. Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol. 2007 Nov 20;25(33):5287-312.

36. Duffy MJ, Harbeck N, Nap M, et al. Clinical use of biomarkers in breast cancer: Updated guidelines from the European Group on Tumor Markers (EGTM). Eur J Cancer. 2017 Apr;75:284-298.