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Comparative Prognostic Significance of CEA and CA15-3 in Breast Cancer

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***Abstract:** Breast cancer is a leading cause of cancer-related mortality worldwide, particularly among women. Thus, it is critical to have reliable biomarkers for prognosis and metastasis detection. This retrospective study compared the prognostic utility of serum tumour markers CEA and CA15-3 in 117 female breast cancer patients admitted to Lattakia University Hospital. Patients were stratified by histopathological type, molecular subtype, tumour stage, size, and metastasis location. Patients were stratified by histopathological type, molecular subtype, tumour stage, size, and metastasis location. Elevated CA15-3 levels were significantly associated with advanced tumour stage (P<0.05) and metastatic disease (P<0.0001), but not with specific metastatic sites, tumour size, or molecular subtype (P>0.05). In contrast, while CEA levels were not significantly elevated in advanced tumour stages, they correlated with larger tumour size (P<0.05) and metastasis (P<0.001), particularly liver metastasis (P<0.05).Kaplan-Meier analysis revealed that elevated CEA (>5 ng/mL) was significantly associated with worse 5-year overall survival (27% vs. 68%, P<0.001), whereas CA15-3 (>35 IU/mL) was not (50% vs. 75%, P>0.05). These findings highlight CEA's potential as a prognostic biomarker, particularly for liver metastasis. The controversial results of our study support using CEA in clinical surveillance for breast cancer.**

***Keywords:** Breast Cancer, Ca15-3, Cea, Prognostic Biomarkers*

Nomenclature:
AJCC: American Joint Committee on Cancer
CA15-3: Carbohydrate Antigen 15 3
CEA: Carcinoembryonic antigen
CRC: Colorectal Cancer
ER: Estrogen Receptor
IDC: Invasive Ductal Carcinoma
IDLC: Invasive Ductal and Lobular Carcinoma
ILC: Invasive Lobular Carcinoma
PR: Progesterone Receptor

I. INTRODUCTION

Breast cancer is the second most frequently diagnosed malignancy around the world, with approximately 2.3 Million new cases reported worldwide, according to GLOBOCAN (2022) [1]. Breast cancer is the most commonly diagnosed cancer and the leading cause of death among female patients [2]. In Syria, breast cancer accounted for about 4,100 new cases in 2022 among females, representing 35% of all female cancer cases [3].

Breast cancer is a heterogeneous disease classified histologically into invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC). IDC is the most common histologic subtype, accounting for 70–80% of all breast cancer cases, whereas ILC occurs in 5–15% of patients [4]. Additionally, there exists a mixed subtype known as mixed invasive ductal and lobular carcinoma (IDLC), which represents 3–5% of breast cancer cases. This variant exhibits both ductal and lobular morphological features, with the ductal component constituting 10–49% and the lobular component comprising at least half of the tumour [5].

As outlined in the 8th edition of the American Joint Committee on Cancer (AJCC) guidelines, breast cancer staging is categorised into two tables: the anatomic staging system, known as the TNM classification, and the prognostic staging system, which is based on molecular subtypes [6].

The anatomic staging system includes three key parameters: primary tumour size (T), regional lymph node involvement (N), and distant metastasis (M), as determined by clinical examination and/or pathological analysis. These three categories are combined to determine the overall five anatomic stages (0, I, II, III, IV) [7]. Stage 0 represents non-invasive breast cancer, while stages I and II indicate early invasive breast cancer. The last two stages involve more advanced disease with poorer prognosis and metastasis [8].

The prognostic staging system is not based on the histological features of the tumour but instead on the expression of three molecular receptors (ER, PR, HER2), which define four distinct subtypes: Luminal A, Luminal B, HER2-enriched, and Triple-Negative Breast Cancer [9]. Luminal A tumours are ER-positive and/or PR-positive and HER2-negative. This subtype has a good prognosis, as it is a low-stage, slow-growing tumour. On the other hand, Luminal B tumors are of a higher stage and have a poorer prognosis. This subtype is ER-positive and/or PR-positive, with or without HER2 receptors. Additionally, the Luminal B subtype is characterized by high expression of the marker of proliferation (Ki-67) [10]. The HER2-enriched subtype is characterised by high HER2 expression in the absence of ER and PR. HER2-enriched cancers grow faster than luminal cancers and have a worse prognosis. Triple-negative breast cancer (TNBC) is negative for ER, PR, and HER2, and has the worst prognosis among all subtypes [11].

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Carbohydrate Antigen 15 3 (CA15-3) is a transmembrane glycoprotein encoded by the *muc1* gene. CA15-3 is considered a key biomarker for detecting cancer progression and metastasis, due to its overexpression in many cancers [12]. Elevated serum CA15-3 values at diagnosis are associated with higher breast cancer stage, tumour size, positive axillary lymph nodes, and worse overall survival [13].

CEA is a glycoprotein primarily expressed during fetal development, with minimal production after birth. Adults may have elevated CEA levels in several pathological conditions. CEA is most commonly used as a tumour biomarker for monitoring colorectal cancer (CRC) recurrence [14]. Furthermore, CEA has also been used as a tumour marker for many tumours, such as lung, uterine, and ovarian cancers [15].–CEA is used in breast cancer patients for surveillance after surgery and monitoring in the advanced stage [16]. CEA, CA 15-3, and CA 27-29 may be used as adjunctive assessments to contribute to decisions regarding therapy for metastatic breast cancer [17]. However, CEA has not been widely investigated as a prognostic biomarker for breast cancer and metastasis. Thus, our study aims to examine the predictive utility of CEA compared with CA 15-3.

II. MATERIALS AND METHODS

We conducted a retrospective study on 117 female patients diagnosed with breast cancer at the oncology department of Lattakia University Hospital. We analysed the medical records of patients, which were selected based on the availability of complete clinical and laboratory data, including tumour marker results (CA 15-3 and CEA), histopathological tumour type, stage, size, presence and location of metastases, as well as estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor status. Records lacking essential data or containing unclear laboratory results were excluded to ensure the reliability of statistical analysis. Concurrent bilateral breast cancers, and male breast cancers were excluded from the study. We obtained the official approval from the institutional ethics committee, and full compliance with patient confidentiality and data privacy was maintained throughout data collection and analysis.

III. STATISTICAL ANALYSIS

The Shapiro-Wilk test was used to assess the normality of continuous variables. Categorical variables were presented as counts and percentages, while continuous variables were reported as mean ± standard deviation or median and interquartile range (25th–75th percentile). The Mann-Whitney test was used for continuous variables. Correlations were evaluated using Pearson's correlation test. To determine the prognostic utility of CEA compared with CA15-3, we conducted Kaplan-Meier analyses and log-rank tests. Results were considered statistically significant when $P < 0.05$. All statistical analyses were performed using the R statistical programming language.

IV. RESULTS

The study included 117 female patients diagnosed with breast cancer, with a mean age of 51.6 ± 11.8 years. The majority of patients (n=108, 92%) were diagnosed with invasive ductal carcinoma (IDC), while invasive lobular carcinoma (ILC) accounted for 8% (n=9) of cases. Patients were further categorised by tumour stage, tumour size, and the presence and location of metastasis. Additionally, the cohort was stratified into the four molecular subtypes of breast cancer—Luminal A, Luminal B, HER2-positive, and triple-negative—based on the expression status of estrogen receptor (ER), progesterone receptor (PR), and HER2 receptor, as detailed in tables 1 to 4. The levels of CA 15-3 and CEA were analysed in patients, as detailed in Table 5.

Table 1: General Characteristics of the Study Population

Characteristic		Values n (%)
Tumor Type	IDC	108 (92.3%)
	ILC	9 (7.7%)
Tumor Stage	I	1 (1.2%)
	II	57 (67.9%)
	III	25 (29.8%)
	IV	1 (1.2%)
Tumor Size	T1	6 (7%)
	T2	61 (70.9%)
	T3	12 (14%)
	T4	7 (8.1%)
Metastasis	Metastatic	76 (81%)
	Non-Metastatic	18 (19%)

Table 2: Location of Metastasis

Location of Metastasis	Bone	Brain	Liver	Lung
n (%)	55 (73.3%)	4 (5.3%)	28 (37.3%)	21 (28%)

Table 3: Tumor Biomarker Status

Type	Positive n (%)	Negative n (%)
Estrogen Receptors	49 (53.8%)	42 (46.2%)
Progesterone Receptors	40 (44%)	51 (56%)
HER2 Receptors	63 (69.2%)	28 (30.8%)

Table 4: Subtype

Subtype	Luminal A	Luminal B	HER2-Positive	Triple Negative
n (%)	16 (17.6%)	40 (44%)	23 (25.3%)	12 (13.2%)

Table 5: Levels of CA15-3 and CEA

Biomarker	Values Median (Q1-Q3)	Pearson Correlation
CA 15-3 IU/ml	57.7 (25-208)	0.7 (*P*<0.01)
CEA ng/ml	10.13 (2.59-37.26)	

A. Relationship between CA15-3 Levels and the Tumour Parameters

CA15-3 levels were measured several times upon admission, so we calculated the mean for each patient and compared it with the research variables. We found that CA15-3 levels were significantly higher in patients with advanced-stage

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disease than in those with early-stage disease ($P<0.05$). Furthermore, CA15-3 values were elevated in with larger tumor sizes, but without significant differences ($P>0.05$). We also found that metastatic patients had significantly higher CA15-3 levels than non-metastatic patients ($P<0.01$). However, there was no significant difference in CA 15-3 levels by metastasis location or breast cancer subtype ($P > 0.05$; Table 6).

Table 6: Levels of CA15-3 Across Study Parameters

Characteristics		CA15-3 Values	*P* Value
Tumor Stage	I+II	33 (21-84.3)	0.023
	III+IV	84.52 (41.95-253)	
Tumor Size	T1	26 (22.7-42.3)	0.68
	T2	38.8 (21.-126.7)	
	T3	39 (25.2-299.1)	
	T4	65.4 (38.9-87.5)	
Metastasis	Metastatic	57.78 (28.5-226.4)	<0.0001
	Non-metastatic	16.9 (14-30.1)	
Bone Metastasis	yes	57.86 (33-312.8)	0.706
	no	73.25 (27.34-196)	
Brain Metastasis	yes	219.7 (34-551.2)	0.65
	no	57.86 (30-216.5)	
Liver Metastasis	yes	113.3 (43.7-243.3)	0.08
	no	51.58 (27-137.2)	
Lung Metastasis	yes	63 (29.95-247.43)	0.995
	no	57.78 (31.5-201.37)	
Subtype	Luminal A	171 (22.78-317.74)	0.32
	Luminal B	34.8 (22.44-92.38)	
	Triple-negative	37.8 (22.9-59.48)	
	HER2-positive	39.9 (26.78-96.6)	

B. Relationship between CEA Levels and the Tumour Parameters

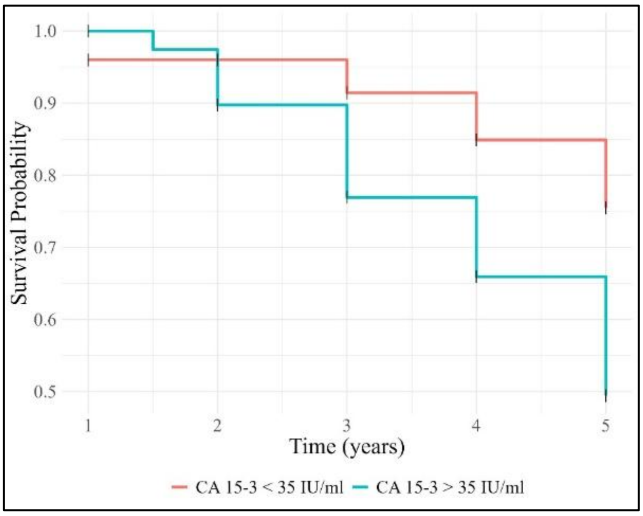
CEA levels were measured several times upon admission, so we calculated the mean CEA level for each patient and compared it with the research variables. We found higher CEA levels in patients with advanced disease, but the difference was not significant ($P>0.05$). We found that larger tumours, especially T3 tumours, were associated with a notable increase in CEA levels ($P<0.05$). Metastatic patients had significantly higher CEA levels than non-metastatic patients (P<0.01). Regarding metastasis location, CEA levels do not appear to be associated with metastasis to the lungs, bones, or brain ($P>0.05$). However, CEA levels were significantly elevated in patients with liver metastasis ($P<0.05$). There was no significant difference in CEA values between the subtypes of breast cancer ($P>0.05$). Table 4 demonstrates the relationship between CEA levels and the tumor parameters.

Table 7: Levels of CEA Across Study Parameters.

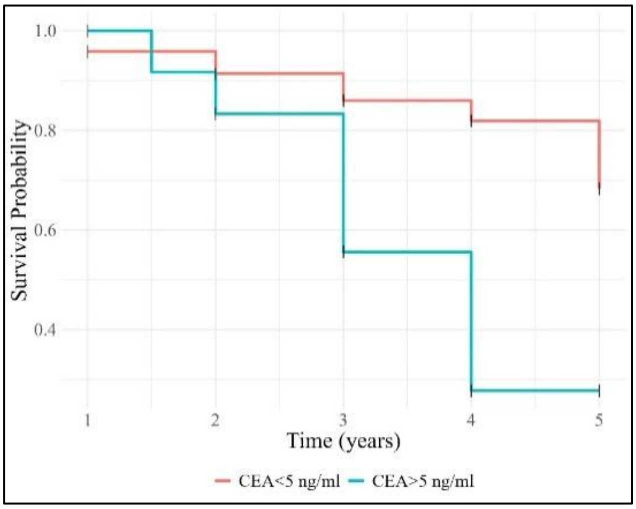
Characteristics		CEA Values	*P* Value
Tumor Stage	I+II	4.55 (1.83-31.8)	0.2
	III+IV	8.6 (2.66-119.7)	
Tumor Size	T1	3.2 (2.58-4.08)	0.024
	T2	12 (2.02-34.24)	
	T3	22.08 (5.84-120.79)	
	T4	3.3 (1.37-8.65)	
Metastasis	Metastatic	12.6 (4.26-51.3)	0.00017
	Non-metastatic	1.81 (1.2-3)	
Bone Metastasis	yes	18.4 (3.4-101.96)	0.239
	no	9.62 (6.22-18.35)	
Brain Metastasis	yes	276.45 (16.81-546.75)	0.13
	no	12.55 (4.14-51.08)	
Liver Metastasis	yes	32.8 (7.9-119.9)	0.023
	no	9.73 (3.8-28.2)	
Lung Metastasis	yes	12.5 (2.78-90.3)	0.77
	no	13.2 (4.52-46.85)	
Subtype	Luminal A	14.75 (2.75-62.4)	0.47
	Luminal B	4.48 (1.92-26.2)	
	Triple-negative	5.27 (1.46-11.55)	
	HER2-positive	12.5 (3.56-40.65)	

C. The Prognostic Significance of CEA Compared to CA15-3 in Breast Cancer

Among the dead patients, the 5-year survival rate among the patient cohort was 60%. To evaluate the impact of CA15-3 and CEA levels on 5-year survival, patients were stratified into groups based on the prognostic cut-off values: 35 IU/mL for CA15-3 and 5 ng/mL for CEA. Analysis revealed that patients with CA15-3 levels exceeding 35 IU/mL had a lower 5-year survival rate than those with lower levels, but the difference was not significant (P > 0.05; Figure 1). Patients with CEA levels above 5 ng/mL had a significantly lower 5-year survival rate than those with lower levels (P<0.001), as shown in Figure 2.



[Fig.1: Kaplan-Meier Survival Analysis by CA15-3 Levels (Log-Rank *P*:0.1)]



[Fig.2: Kaplan-Meier Survival Analysis by CEA Levels (Log-Rank *P* <0.001)]

V. DISCUSSION

We found that CA15-3 levels were significantly elevated in patients with III and IV tumours compared with those with I and II tumours ($P<0.05$). Similarly, CA15-3 levels increased with larger tumour size, but this result did not reach statistical significance (P>.05). Furthermore, metastatic patients had significantly higher CA15-3 levels than the non-metastatic group ($P<0.01$). As noted, CA15-3 is used as a biomarker for breast cancer progression. Our findings align with multiple studies, including a 2014 study by Hashim *et al.* in Iraq, which reported significantly elevated CA15-3 levels in advanced-stage tumors, and a 2021 study by Uygur *et al.* in Turkey, which demonstrated substantially higher CA15-3 values in patients with metastatic breast cancer [18, 19].

Regarding metastatic sites, no significant differences in CA 15-3 values were observed among bone, liver, lung, and brain metastasis ($P>0.05$). Although some studies have shown that CA15-3 levels are higher in breast cancer patients with certain types of secondary metastasis—such as Baqir *et al.,* who found elevated CA15-3 in cases of bone metastasis—others, like Fakhari *et al.,* reported no association between CA15-3 and secondary metastasis [20, 21]. This might reflect the conflicting results regarding the association between CA15-3 and secondary metastasis in breast cancer patients. As mentioned, CA 15-3 is derived from the MUC1 gene product, which is overexpressed in many cancers and metastases, leading to elevated CA 15-3 levels [22].

We found that CA 15-3 levels were significantly increased in Luminal A patients. Similar to our findings, Sinha *et al.* showed that elevated CA15- 3 levels were most frequently seen in luminal subtypes, while they were less common in the HER2-enriched subtype [23]. Also, Salih *et al.* demonstrated that luminal breast cancer patients have a higher likelihood of elevated CA15-3 levels at relapse than patients with HER2-enriched and basal-like breast cancers [24]. This can be attributed to the higher expression of the MUC1 protein in luminal subtypes compared to others, as CA15-3 is derived from proteolytic cleavage of MUC1's extracellular domain [25].

We found that CEA levels were not significantly elevated in patients with advanced stages ($P>0.05$). However, CEA levels increased substantially with larger tumour size ($P<0.05$). Furthermore, metastatic patients had significantly higher CEA levels than the non-metastatic group ($P<0.01$). Shao et al. demonstrated that patients with elevated CEA and CA15-3 levels had larger tumours, more advanced axillary lymph node involvement, and higher TNM stage [26]. Also, Luan et al. found that CEA levels were elevated in patients with the most advanced stages and larger tumours [27].

Our study showed significantly higher CEA levels in patients with liver metastasis compared with those without ($P<0.05$). In fact, overexpression of CEA is closely associated with liver metastasis. CEA triggers Kupffer cells to produce pro-inflammatory cytokines, which creates a favourable hepatic micro-environment for cancer cell implantation [28]. This process occurs when CEA interacts with a specific receptor on Kupffer cells, promoting hepatic metastatic initiation and facilitating the mesenchymal-epithelial transition (MET) of circulating tumor cells in the liver [29].

The OS of patients with high CEA levels (CEA-high: n = 61, 5-year OS 27%) was significantly worse ($P<0.001$) than that of CEA-low patients (n = 43, 5-year OS 68%). There was no significant difference in OS ($P>0.05$) between CA15-3-high and CA15-3-low patients (n=66 and n = 37, respectively; 5-year OS 50 vs. 75%). Our findings demonstrated that CEA might be a useful prognostic biomarker for breast cancer patients. Our study was similar to Imamura et al., who found that CEA and CA15-3 levels might help predict the prognosis of patients with breast cancer irrespective of the subtype [30]. However, unlike the Imamura study, we did not find a statistically significant association between CA15-3 levels and 5-year OS. The Imamura study supports the use of CEA and CA15-3 as prognostic biomarkers. However, our study showed that CEA rather than CA15-3 is a better prognostic biomarker for breast cancer.

This study has several limitations. First, CA 15-3 and CEA analyses were performed in different laboratories, which may have introduced modest variations in biomarker measurements due to inter-laboratory differences in protocols and calibration. Second, the results lack a comprehensive screening and diagnostic panel for breast cancer, potentially limiting the broader clinical applicability of our findings. Finally, the retrospective nature of the study design may weaken the conclusions; a prospective study would allow for better-controlled investigations and more robust validation of the results. Also, large-scale studies that include treatment regimens among patients would be advisable, as they would provide stronger outcomes.

VI. CONCLUSION

In conclusion, our study demonstrates that both CA15-3 and CEA levels were significantly elevated in metastatic breast cancer, with CEA showing a specific increase in liver metastasis. In addition, we found that patients with high levels of CEA _rather than CA15-3_ have significantly worse OS, reflecting better prognostic utility than CA15-3.

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DECLARATION STATEMENT

After aggregating input from all authors, I must verify the accuracy of the following information as the article's author.

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- **Ethical Approval and Consent to Participate:** The content of this article does not necessitate ethical approval or consent to participate with supporting documentation.
- **Data Access Statement and Material Availability:** The adequate resources of this article are publicly accessible.
- **Author's Contributions:** The authorship of this article is contributed equally to all participating individuals.

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