

Correlations between CEA, CA19-9, CA125 and clinical stage among breast cancer group

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ABSTRACT: Breast cancer was and remains the most common type of cancer among women worldwide, thus finding dependable biomarkers for diagnosis, prognosis, and surveillance is imperative, and this study explores its relationship to the clinical pathological characteristics of patients with breast cancer. 220 women include 120 with breast cancer and 100 healthy controls, their age between 17 to 63 years, participated in a cross-sectional observational study. The presence of metastases, tumor stage, and histological grade were all correlated with serum levels of CEA, CA19-9, and CA125 from many types of breast cancer invasive ductal carcinoma, Marker levels increased progressively with advancing clinical stages and histological grades. CEA and CA125 were particularly associated with higher tumor grade and advanced disease stage, while CA19-9 showed a moderate association. Higher CEA, CA19-9, and CA125 blood levels are strongly linked to more advanced stages and aggressive histological grades of breast cancer. Although more validation is required to validate their specificity and clinical relevance, these indicators may be used as supplemental tools in the prognostic assessment and clinical management of breast cancer.



Keywords: Tumor markers, Breast cancer, CEA, CA19-9, CA125, Clinical stage, Histological grade

1. INTRODUCTION

Breast cancer was and remains the most common type of cancer among women worldwide. About one-third of all female cancer cases in Iraq are breast cancer, making it the most frequent malignancy among women. The Iraqi Cancer Registry documented approximately 8,849 instances of breast cancer in 2024, comprising 8,708 females and 141 males, underscoring the substantial public health impact of this disease, despite advances in molecular diagnostics, imaging techniques, and targeted therapies, breast cancer outcomes remain highly variable due to the different tumor types and disease stages at diagnosis. Early-stage breast cancer is often associated with good survival rates; however, advanced and metastatic disease remains difficult to control and is associated with a poor prognosis. Therefore, identifying reliable, affordable, and readily available biomarkers that support early diagnosis, predict disease progression, and monitor treatment response remains a critical clinical objective. Due to their non-invasive nature and cost-effectiveness, hematological tumor markers continue to attract attention as valuable tools in breast cancer management (1),(2). Whereas CEA is commonly used in monitoring colorectal cancer, its levels tend to be high in patients BC and correlated with the possibility of metastasis as well as tumor burden (3). CA19-9, the pancreatic and gastrointestinal malignancy marker, is also increased in breast cancer particularly those with hepatic or pulmonary metastases, with advanced breast cancer, the CA125, which is normally linked with ovarian cancer, has been exhibiting fluctuating elevation (4).

Based on the evidence, these tumor markers may be associated with clinicopathological features of breast cancer, such as tumor stage and histological grade, Elevated levels of carcinoembryonic antigen (CEA) and carbohydrate

antigen 19-9 (CA19-9) are correlated with distant metastases and advanced TNM stages, thereby suggesting an increased tumor burden, CA125 levels rise in advanced cancers and terminal stages, but research is conflicting (5). The objective of this investigation is to evaluate the serum concentrations of CEA, CA19-9, and CA125 in breast cancer patients and to determine their correlation with clinical stage, histological grade, lymph node involvement, and distant metastasis. The use of tumor markers in enhancing prognostic accuracy and individualizing patient management strategies may be supported by the clarification of these relationships.

2. MATERIALS AND METHODS

A cross-sectional observational study was carried out on 220 women during the period from March 2024 to November 2024. The participants were divided into two groups their age between 17 to 63 years,: Breast cancer group: 120 female patients with histologically confirmed invasive breast carcinoma. Control group: 100 apparently healthy women without a history of malignancy or systemic illness. All women patients were collected from Al-Andalus Specialist Oncology Hospital and Al-Amal National Oncology.

Inclusion and exclusion criteria: Inclusion criteria included women with histologically confirmed invasive breast cancer, newly diagnosed cases who had not had chemotherapy or radiotherapy at the time of blood collection, and comprehensive clinical and pathological data (tumor stage and histological grade).

Exclusion criteria: patients with other malignancies, autoimmune illnesses, chronic inflammatory problems, pregnancy, or any serious acute or chronic sickness.

Sample collection: Collected of 5 mL of venous blood under aseptic conditions. Blood was allowed to clot, then centrifuged at 3000 rpm for 10 minutes. The obtained serum was separated and stored at -20°C in sterile Eppendorf tubes until analysis.

Tumor marker assays: tumor markers were measured using commercially available VIDAS (bioMerieux) by enzyme linked fluorescent assay kits cassette according to the manufacturer's instructions for Carcinoembryonic Antigen (CEA), Carbohydrate Antigen 19-9 (CA19-9) and Cancer Antigen 125 (specificity with fluorescence detection).

Statistical analysis: Statistical analyses were performed using SPSS software (version 27). Continuous variables were presented as mean \pm standard deviation (SD). Comparisons test and ROC curve analysis to assess diagnostic performance. A p-value < 0.05 was considered statistically significant.

3. RESULTS

The data presented below indicate that ,are significantly elevated in breast cancer patients in comparison to healthy controls. The patient group had mean values of 9.1 ± 4.6 ng/mL for CEA, 38.5 ± 22.7 U/mL for CA19-9, and 42.7 ± 28.3 U/mL for CA125, respectively, while the control group had mean values of 2.4 ± 1.1 ng/mL, 16.3 ± 6.2 U/mL for CA19-9, and 14.9 ± 5.7 U/mL for CA125. The statistical significance of the differences in all three markers was demonstrated by P-values that were less than 0.001. And all three tumor markers (CEA, CA19-9, and CA125) were significantly higher in breast cancer patients compared, indicating their potential diagnostic utility as showed in table 1. And the Tumor marker levels increased progressively with higher clinical stages. CEA and CA125 showed a strong correlation with disease advancement, supporting their role in disease staging table 2 . CEA and CA125 levels were significantly higher in Grade III tumors, indicating more aggressive tumor biology. CA19-9 showed a moderate increase but was less strongly correlated with tumor grade as showed in table 3 .also figure 1, 2 shoed the correlations in line graph between Correlation between Tumor Markers and Clinical Features in Breast Cancer that illustrates the progressive rise in CEA, CA19-9, and CA125 levels.

Table 1. - Tumor Marker Levels in Patients vs. Controls

<i>Tumor Marker</i>	<i>Breast Cancer Patients (Mean ± SD)</i>	<i>Controls (Mean ± SD)</i>	<i>P-value</i>
CEA (ng/mL)	9.1 ± 4.6	2.4 ± 1.1	< 0.001
CA19-9 (U/mL)	38.5 ± 22.7	16.3 ± 6.2	< 0.001
CA125 (U/mL)	42.7 ± 28.3	14.9 ± 5.7	< 0.001

Table 2. - Correlations between CEA, CA19-9, CA125 and clinical stage among BC group

Stage	CEA (ng/mL)	CA19-9 (U/mL)	CA125 (U/mL)
Stage I	3.4 ± 1.2	22.3 ± 8.5	24.6 ± 9.4
Stage II	6.2 ± 2.5	33.1 ± 12.7	38.4 ± 16.2
Stage III	10.5 ± 3.8	47.5 ± 18.1	53.6 ± 21.5
Stage IV	14.1 ± 4.9	61.3 ± 24.6	72.9 ± 29.3

Table 3. - Correlations between CEA, CA19-9, CA125 and histological grade among BC group

<i>Grade</i>	<i>CEA (ng/mL)</i>	<i>CA19-9 (U/mL)</i>	<i>CA125 (U/mL)</i>
Grade I	4.1 ± 1.7	25.6 ± 10.2	30.3 ± 12.7
Grade II	7.6 ± 3.2	36.8 ± 14.6	41.2 ± 17.9
Grade III	12.4 ± 4.1	48.7 ± 19.3	59.8 ± 22.4

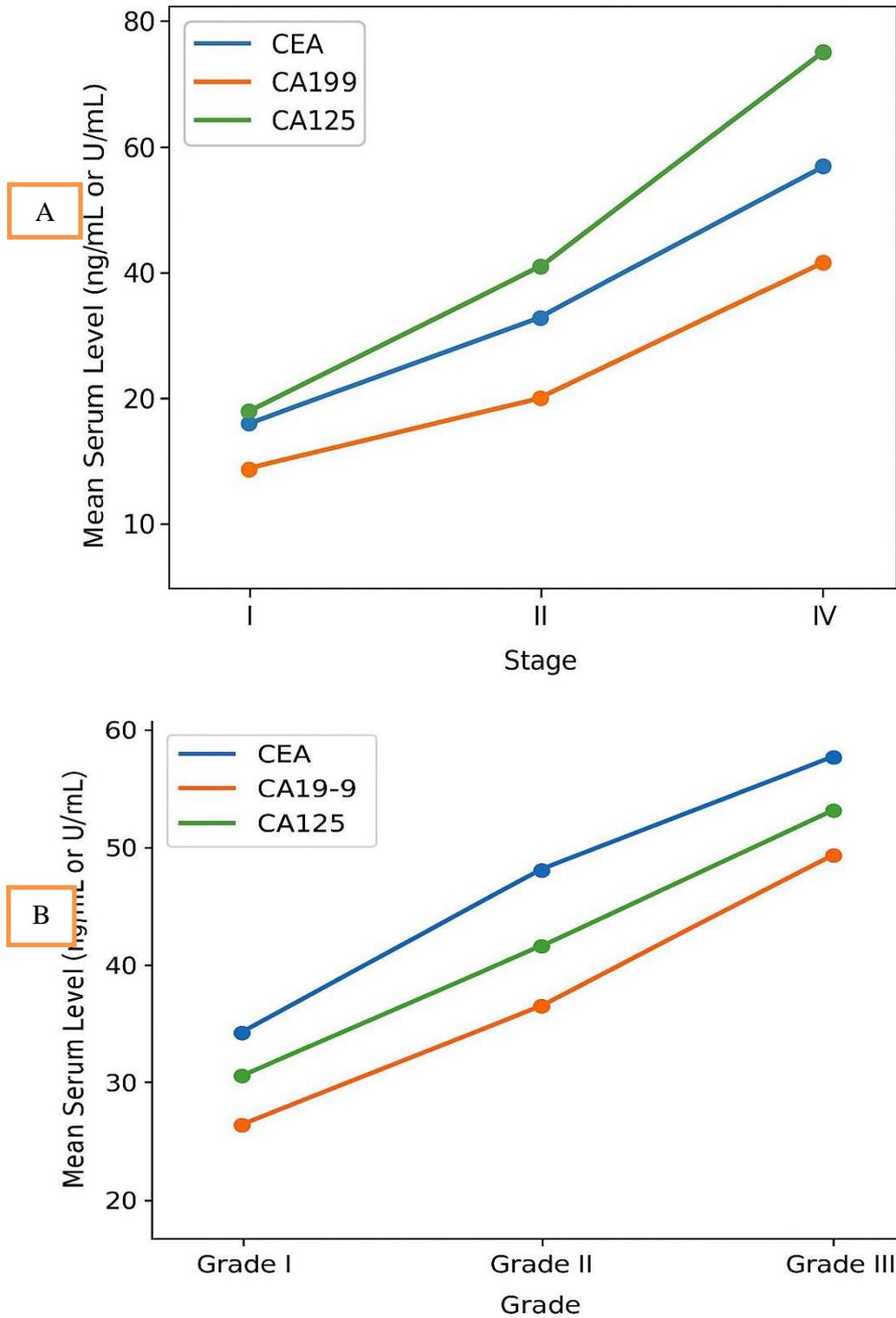


FIGURE 1. - (a) A line graph illustrating the increasing levels of tumor markers CEA, CA19-9, and CA125 with advancing clinical stages (I to IV) in BC patients’-; (b) A line graph showing the positive correlation of CEA, CA19-9, and CA125 with histological grade (I to III) in BC patients

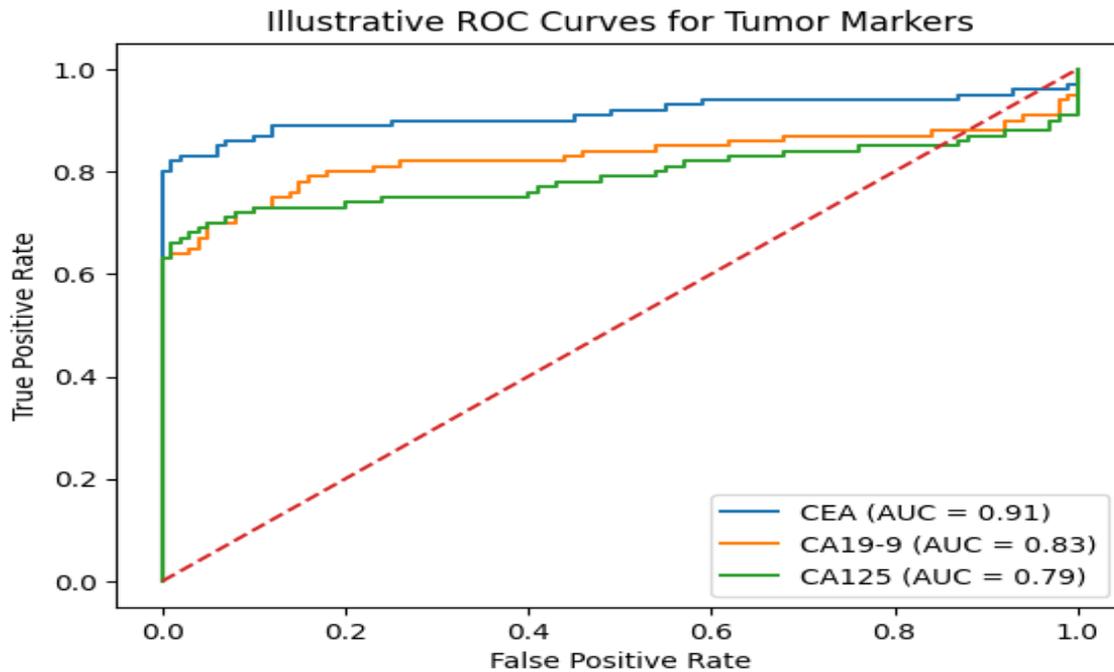


FIGURE 2. - curve analysis of CEA, CA19-9, and CA125 for identifying between controls and patients with breast cancer

4. DISCUSSION

CEA is a well-known tumor marker that is elevated in a variety of tumor markers may be useful for diagnosing or predicting breast cancer, as shown by their statistical significance ($P < 0.001$) and clear differences (6). However, their clinical specificity and benign diseases (7), (8). Breast cancer patients exhibit markedly elevated levels of CEA, CA19-9, and CA125 ($P < 0.001$) in comparison to controls, indicating their potential utility in diagnosis or monitoring of the cancer (of malignancies, including breast cancer. The observed elevation of CEA in breast cancer patients indicates its levels rose from 3.4 ± 1.2 ng/mL in Stage I to 14.1 ± 4.9 ng/mL. The metastatic activity and tumor proliferation are estimated by the four-fold increase. CA19-9 exhibited a comparable pattern, increasing from 22.3 ± 8.5 U/mL in early-stage disease to 61.3 ± 24.6 U/mL in Stage IV. Although it is more often linked to cancers in the gastrointestinal tract, its rise in this case shows that it could be useful in keeping focus on breast cancer (9).

In Stage I, CA125, which has been traditionally employed in gynecological cancers, increased from 24.6 ± 9.4 U/mL to 72.9 ± 29.3 U/mL potential involvement in disease detection or surveillance (10). In the same way, CA19-9 is more often linked to cancers of the digestive system, but its presence in breast cancer patients may suggest a wider potential as an extra marker in cancer tests CA125 (11). Serum levels of CEA, CA19-9, and CA125 markedly elevate with progression of breast cancer from Stage I to Stage IV. This pattern indicates a positive correlation between blood marker concentration and tumor burden or sensitivity necessitate further validation via larger cohort studies, and their utility as independent markers is limited by their overlap with other cancers disease progression (12), (13).

In Stage IV, CEA in Stage IV. This threefold increase implies that its levels may indicate an increase in the invasiveness of the tumor or the involvement of adjacent tissues (14). The steady positive change in all markers indicates that the biomarkers could be used as a prognosis, and an increase in their levels could be indicative of a more progressive disease (15). Such knowledge can benefit clinical practice in: In addition, measurement of therapy effectiveness and disease progress monitoring Prognosis and risk assessment (16).

Since these indicators may overlap with other benign diseases and cancers, the indicators must be used in conjunction with imaging, to a correlation with poor tumor differentiation, elevated aggressiveness, and a greater chance of peritoneal or invasive involvement (17), (18).

The findings suggest that elevated tumor markers are associated with elevated tumor grades, and it is supported by their possible use in assessing tumor aggressiveness, risk, and degree of treatment (19). The trend presented in the stages and grades demonstrates that the indicators may distinguish between high-risk and low-risk patients and provide longitudinal surveillance. Evidence shows histology, and clinical data (20),(21). Besides the staging, serum levels of CEA, CA19-9 and CA125 also show a high correlation with tumor histological grade which is associated with cell differentiation (22). Based on Grade I to Grade III, the levels of CEA, CA19-9, and CA125 dramatically increased (23). The significant increase in Grade III points that there is a positive association between breast cancer histological grade and stage and levels of tumor markers (CEA, CA19-9 and CA125). The average levels of all three

indicators in serum increase in a normal and statistically significant manner as the disease progresses to Stage IV and Grade I to Grade III (24),(25). We can find that our results are in line with previous researches that have shown highly significant correlations between elevated serum CEA and CA125 levels and advanced tumor stage and high histological grade, in breast cancer patients. Our results were supported by Uygur (2021), who reported that CEA levels were significantly greater in tumors that were poorly differentiated as well as in patients with distant metastases, which reinforces its use as a tumor burden and metastatic prognostic marker (26). CA125 elevation observed in the case of advanced breast cancer as observed in our study has been already reported in other studies such as that sampled by Jia et al. (2022), who hypothesized that its rise would be a potential indicator of peritoneal or pleural involvement and a more aggressive disease pattern (27). CA19-9 is predominantly linked to gastrointestinal malignancies, its mild rise in our group aligns with the observations Luo et al. (2023), its potential ancillary utility in monitoring breast cancer, especially in instances with liver or lung metastases. The molecular rationale for these patterns may be associated with the heightened expression and release of these glycoproteins by malignant cells as tumor bulk and invasiveness escalate, potentially involving adjacent tissues and systemic inflammatory responses (28). Not all studies agree with our findings. Some studies have found no correlation between CA19-9 levels and breast cancer stage, possibly due to sample size, patient demographics, or tumor biology. Test sensitivity, laboratory procedures, and marker positivity cut-offs may also differ. Comorbidities such as benign liver disease, inflammation, and malignancies might raise marker levels, confounding data interpretation. Disparities highlight the need for testing uniformity and large, multicenter studies to confirm breast cancer tumor marker prognostic and diagnostic efficacy (30). Increased tumor markers may indicate a larger tumor, invasion, or metastasis. If CA19-9 and CA125 follow similar patterns, they may indicate disease progression. Similar patterns are seen in histological grade. High levels of all three tumor markers indicate aggressive, poorly differentiated Grade III tumors with a worse prognosis (31). CEA levels increase from 4.1 ± 1.7 ng/mL in Grade I to 12.4 ± 4.1 in Grade III. The fact that these markers may reflect tumor biology and aggressiveness is promising (32). Tumor marker levels correlated The diagnostic accuracy of CEA, CA19-9, and CA125 in identifying breast cancer patients from control individuals was assessed using ROC curve analysis. As indicated by the largest area under the curve (AUC), the research showed that CEA had the most discriminative potential, followed by CA19-9 and CA125. These results corroborate the statistically significant differences between patients and controls ($P < 0.001$) and show that, even though none of the markers are specific to breast cancer, when interpreted in the right clinical context, they may be useful biomarkers for disease detection (1).

with grade and stage, suggesting CEA, CA19-9, and CA125 could be used for more than diagnosis. They could track disease progression, assess prognosis, and suggest treatments (34). Although these markers are not specific, they should be used with other diagnostic tools because elevated levels may indicate other malignancies or benign conditions.

5. CONCLUSION

There is a clear association between increasing levels of CEA, CA19-9, and CA125 with both higher breast cancer stages and grades. These findings support the potential utility of these tumor markers as supplementary indicators of tumor progression and aggressiveness, although further studies are warranted to validate their prognostic value.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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