RESEARCH ARTICLE

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# Exploring the Prognostic Value of CS15-3 Tumor Marker in Breast Cancer Recurrence

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## Abstract

**Background:** The most prevalent tumor marker for breast cancer is CS15-3. This marker's elevated serum levels have been proven to predict a patient's risk of developing the condition again. **Purposes:** The purpose of this study was to ascertain the sensitivity of blood CS15-3 levels in the identification of breast cancer recurrence. **Patients and methods:** A prospective cohort follow-up analytical study was conducted at Basra Oncology Center from early 2016 to the end of 2022. The study included 178 females aged ≥18 years with histologically confirmed invasive ductal breast cancer. CS15-3 had been evaluated for all included cases on two occasions: the first, at the time of diagnosis or remission, and the second, at the time of progression. The tumor marker (CS15-3) was evaluated using a Cobas e411 analyzer (Roche Diagnostics International Ltd). **Results:** The mean age showed no significant difference between the groups (P=0.581). The duration of progression was higher among those with the luminal group (40.60± 42.08). Those with bony and liver metastasis were mostly among luminal (50.0%) and HER 2+ (52.4%) groups respectively. At the time of diagnosis CS15-3 tumor marker showed no significant difference between the three groups, while at the time of progression, the luminal group showed higher means (120.74± 95.07) compared to others with a significant mean difference of (-99.84± 94.43). **Conclusions:** Age, disease stages, and co-morbidity have no significant influence on the distribution between groups of luminal. The duration of progression was higher among those in the luminal group. Osseous and hepatic secondaries are mostly among luminal and hormonal receptors positive. Initially, at the time of diagnosis CS15-3 marker expressed no significant difference between the groups, whereas at the time of progression, the luminal group expressed a higher means of level of the CS15-3 marker.

**Keywords:** CS15-3- HR expression- Triple- negative- breast cancer- hormonal receptors

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## Introduction

According to estimates, breast cancer is the most prevalent cancer among women worldwide and the main cause of cancer-related deaths [1]. According to reports, advanced countries have a higher incidence of breast cancer than developing countries, although this disparity may be explained by the superior diagnostic techniques that are available in developed countries. In reality, an epidemiological study from Iraq found that over the past few years, the incidence of breast cancer has been rising in Iraq [2]; as many as 17.6% of patients with cancer that were registered in Basra, Iraq, had breast cancer [2].

According to the immunohistochemical expression of hormone receptors, breast cancer has various molecular subtypes, triple-negative (TNBC), which lacks the expression of any of receptors, progesterone receptor positive (PR+), human epidermal growth factor receptor positive (HER2+), and estrogen receptor-positive (ER+) [3]. The four forms of luminal tumors are luminal A (ER+ and/or PR+, HER2-, Ki-6714 %); luminal B (ER+ and/or PR+, HER2+ and/or Ki-6714 %); HER2 positive (ER- and PR-, HER2+); and triple-negative [4].

With a varied disease-free period that can last anywhere between a few months and decades, about one-third of individuals with locally advanced breast cancer will eventually acquire metastatic illness [5].

The Mucin short variant S1 (MUC1) gene produces the mucinous antigen known as CS15-3. MUC1's purpose is not fully understood, however, it may contribute to cell adhesion by making malignant cells easier to separate, which would promote cancer invasion and metastasis [6]. The majority of individuals with metastatic breast carcinoma had elevated serum levels of CA15-3, the most frequently utilized tumor marker for breast cancer [7]. In patients with locally advanced breast cancer, a steady increase in the serum level of CS15-3 is a reliable indicator of disease progression and recurrence [8, 9]. Additionally, high tumor burden is indicated by elevated CA15-3 in patients with metastatic breast cancer, which

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has a significant impact on survival [10].

Even though the American Society of Clinical Oncology's most recent guidelines do not advise using circulating CS15-3 to check on patients for recurrence after primary breast cancer therapy [11], measuring serum CS15-3 levels is a common clinical practice due to the test's speed, non-invasiveness, reproducibility, and quantitative nature [12]. Studies have demonstrated that increased serum levels of CS15-3 are highly specific for identifying breast cancer relapse [13], but the test's sensitivity varies depending on a variety of variables, including the molecular subtype of the disease, the location of the metastasis, and the number of metastatic sites [14, 13, 15]

In the present study, serum CS15-3 in patients with locally progressed or metastasized breast cancer was correlated with different molecular subtypes of breast cancer. The purpose of this study was to ascertain the sensitivity of blood CS15-3 levels in the identification of breast cancer recurrence.

## Materials and Methods

*Study design and population*

A prospective cohort follow-up analytical study was conducted at Basra Oncology Center from early 2016 to the end of 2022. The study included 178 females aged ≥18 years with histologically confirmed invasive ductal breast cancer stages I, II, and III.

*Ethics*

This study was approved by College of Medicine (No# 1201).

*Exclusion criteria*

We excluded patients with stage IV at presentation, patients with second malignancy, patients with active inflammation, patients with rare histopathological subtypes (other than ductal), and those who refused to be included in the study.

*Patients' follow-up*

All patients who were followed were kept under regular follow-up during the study period (maximum of 6 years) for assessment of disease progression according to the recommended clinical practice. History, physical exams, and laboratory tests (including CA-15-3) were performed every 3–4 months in the first 2 years, and every 6–8 months from 3 to 5 years according to the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) Guidelines. Annual mammography was performed; another testing was directed by the patient's symptoms and the discretion of the treating physician. Regular pelvic ultrasound was performed twice yearly for a patient on adjuvant tamoxifen.

*Tumor marker (CS15-3) evaluation*

CS15-3 was evaluated for all included cases on two occasions: the first, at the time of diagnosis or remission, and the second, at the time of progression. The tumor marker (CS15-3) had been evaluated using a Cobas e411 analyzer (Roche Diagnostics International Ltd).

*Statistical analysis*

Statistical calculations were done using Statistical Package for the Social Sciences version 26 (SPSS Inc.). In which categorical data were expressed as numbers and percentages, and the differences between the groups were analyzed using the Chi-square test (X2) and Fisher exact test. Continuous data expressed as mean± SD and the differences between the groups were analyzed by the one-way ANOVA test for normally distributed data. Shapiro-Wilk test was used to test the normality of the data, and outliers were detected using Boxplot methods. The mean differences of tumor marker (CS15-3) were assessed using a Paired sample t-test. The confidence interval of 95% was applied as the dependent interval in statistics and P-values <0.05 were accepted as statistically significant.

## Results

The mean age showed no significant difference between the groups (P= 0.581). The stages of malignancy and the co-morbidity were presented with no significant difference among the three studied groups (P >0.05). The duration of progression was higher among those in the luminal group (40.60± 42.08) compared with others. Although there was no statistically significant value was recorded. Site of metastasis showed that those with bony and liver metastasis were mostly among luminal (50.0%) and HER 2+ (52.4%) groups respectively. While loco-regional, lung, and brain showed no significant difference among the studied groups (P <0.05), (Table 1).

At the time of diagnosis CS15-3 tumor marker showed no significant difference between the three groups, while at the time of progression, the luminal group showed higher means (120.74± 95.07) compared to others with a significant mean difference of (-99.84± 94.43), (Table 2).

## Discussion

The National Federation of French Cancer Centers declares in their report on the recommendations for the utilization of serum tumor markers in breast cancer that while the sensitivity of tumor markers in the diagnosis of local recurrence is poor, their utility (particularly that of CA 15.3) in early identification of breast cancer metastases is clear [16]. Elevated CS15-3 is a sensitive marker for the early diagnosis of distant metastasis, but not for loco-regional recurrence, according to a recent study by Riedinger et al. (2016) [17].

Recent research has demonstrated a strong correlation between elevated serum CS15-3 levels and the molecular subtype of breast cancer, with luminal breast cancer patients having a higher likelihood of elevated CS15-3 levels at relapse than patients with HER2 enriched and basal-like breast cancers [18, 19]. Due to the mucinous nature of CS15-3, it is believed that the luminal subtype of breast cancer exhibits overexpression more commonly than the less differentiated HER2-enriched and triple-negative basal-like subtypes [20]. The molecular subtype

Table 1. The Demographical Data Analysis among the Molecular Types of Breast Cancer

| Variables | HER 2+ (n= 21) | Luminal (n= 116) | Triple-negative (n= 41) | P-value |
|---|---|---|---|---|
| | | Mean ±SD / No. (%) | | |
| Age (years) (mean± SD) | 49.29± 10.15 | 51.43± 12.28 | 49.54± 12.41 | 0.581 |
| Co-morbidity | | | | |
| Hypertension | 4 (19.0) | 11 (9.48) | 5 (12.19) | 0.09 |
| Diabetes mellitus | 0 | 10 (8.62) | 1 (2.4) | |
| Hypertension and Diabetes mellitus | 1 (4.76) | 8 (6.9) | 5 (12.19) | |
| Staging | | | | |
| I | 2 (9.5) | 3 (2.6) | 3 (7.3) | 0.438 |
| II | 6 (28.6) | 29 (25.0) | 8 (19.5) | |
| III | 13 (61.9) | 83 (71.6) | 28 (68.3) | |
| III-A | 0 | 0 | 1 (2.4) | |
| III-B | 0 | 1 (0.9) | 1 (2.4) | |
| Duration of progression (months) (mean± SD) | 27.10± 26.01 | 40.60± 42.08 | 28.71± 30.52 | 0.118 |
| Mode of progression | | | | |
| Loco-regional | 2 (9.5) | 20 (17.2) | 5 (12.2) | 0.55 |
| Distant | | | | |
| Bone | 3 (14.3) | 58 (50.0) | 15 (36.6) | 0.006* |
| Lung | 8 (38.1) | 44 (37.9) | 16 (39.0) | 0.48 |
| Brain | 2 (9.5) | 5 (4.3) | 4 (9.8) | 0.366 |
| Liver | 11 (52.4) | 25 (21.6) | 17 (41.5) | 0.003* |

*Significant at P-value <0.05

Table 2. The CS15-3 Tumor Marker Analysis among the Molecular Types of Breast Cancer

| Variables | | HER 2+ (n= 21) | Luminal (n= 116) | Triple-negative (n= 41) | P-value |
|---|---|---|---|---|---|
| | | | Mean± SD | | |
| CS15-3 | At the time of diagnosis | 21.90± 6.78 | 20.90± 7.46 | 21.53± 8.15 | 0.803 |
| | At the time of progression | 73.95± 90.82 | 120.74± 95.07 | 71.82± 85.52 | 0.005* |
| | Mean difference | -52.04± 92.08 | -99.84± 94.43* | -50.28± 84.36 | 0.006* |

*Significant at P-value <0.05

of breast cancer in the current study was strongly related to an increase in CS15-3 at relapse ($p< 0.05$). Similar to our findings, Sinha et al. discovered that elevated CS15-3 levels were most frequently seen in luminal subtypes while they were less common in the HER2-enriched subtype [21].

Additionally, the findings of the study by Park et al. demonstrated that CS15-3 elevation was negatively impacted by the HER2-enriched type when compared to the hormone receptor-positive type, regardless of the number of metastases or the existence of pleural or lymph node metastasis [22]. The majority of patients with higher CS15-3 levels had bone, lung, or liver metastases, according to previously published studies [23, 24].

The present study found that most of these sites of recurrence are mostly associated with luminal molecular type than other forms; this is in support of our finding that higher CS15-3 levels at the time of recurrence are associated mostly with luminal molecular type of breast cancer.

In conclusion, age, disease stages, and co-morbidity have no significant influence on the distribution between groups of luminal. The duration of progression was higher among those in the luminal group. Osseous and hepatic secondaries are mostly among luminal and hormonal receptors positive. Initially, at the time of diagnosis CS15-3 marker expressed no significant difference between the groups, whereas at the time of progression, the luminal group expressed a higher means of level of the CS15-3 marker.

## Author Contribution Statement

M. J. Salih; Conceptualization; Methodology; Investigation; Resources; Data Curation; Writing - Original Draft; L. Al-Mansouri; Conceptualization; Methodology;

Resources; Data Curation; Writing - Original Draft; H. M. Hasson; Conceptualization; Investigation; Resources; Data Curation; Writing - Original Draft

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