RESEARCH ARTICLE - MEDICAL TECHNIQUES

Evaluation of Preoperative CA15-3 Level and its Relationship with Clinico-pathological Characteristics in Primary Breast Cancer Patients

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Article Info. Abstract

Article history: Cancer antigen15-3 (CA15-3) is utilized as a tumor marker in breast cancer. In the metastatic situation, it has been regarded as having a predictive role. However, the usefulness of serum CA15-3 in preoperative breast cancer remains argumentative. Therefore, this study aimed to estimate the association of preoperative serum CA15-3 level with the clinico-pathological characteristics in Iraqi women patients with breast tumor and their efficiency for the prediction of primary breast cancer. Preoperative CA15-3 levels were assessed by ELISA technique in 60 Iraqi women with breast tumor (30 with primary breast cancer and 30 with benign breast tumor) before surgery and treatment, as well as 30 healthy controls. In addition, the clinico-pathological characteristics information of all the patients was reported. CA15-3 level showed a significant difference between its level in the sera of primary breast cancer women in comparison to the benign breast tumor women (p<0.001) and healthy control women one (p>0.001). The area under the curve (AUC) of CA15-3 for discriminating patients with primary breast cancer and healthy control subjects was 0.720 (95% CI: 0.589 to 0.828). Furthermore, the present study showed that higher preoperative CA15-3 level was significantly associated with a larger tumor size and lymph node metastasis. This means that elevated CA15-3 is correlated with an increased tumor burden, suggesting its predictive value.

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Keywords: Breast Cancer; CA15-3; Tumor Marker; Predictive Factor.

1. Introduction

Breast cancer is the more frequent female malignancy and the main reason for death. [1]. Serum tumor markers have an essential part in checking, early detection returning of disease, and therapy for a variety of cancers [2]. Cancer antigen 15-3 (CA15-3) is the most extensively utilized serum tumor marker in the management of breast cancer patients [3]. CA15-3 is a member of the mucin-1 (MUC-1) family of glycoproteins [4], is overexpressed in breast cancer cells [5], which plays a role in cells adhesion and interactivity, may promote cancer cell invasion and metastasis [6]. Although it has been documented largely in metastatic breast cancer, elevated CA15-3 levels can be detected in the early stages of the disease [7]. However, the predictive efficiency of preoperative elevations of CA15-3 level in breast cancer remains argumentative.

American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guidelines do not advise using serum CA15-3 for breast cancer checking and therapy [8, 9]. In contrast, The European Group on Tumor Markers has advised the CA15-3 levels to be used for estimating predictive, the early diagnosis of disease advancement, and therapy surveillance in breast cancer [10]. Therefore, the present study aimed to investigate the relation between preoperative serum CA15-3 level and clinico-pathological characteristics, in addition, to the predictive efficacy of this serum biomarker in primary breast cancer.

2. Materials and Methods

2.1. Study design

The study included sixty Iraqi females patients aged (22-80) years suffering from breast tumor (30 with primary breast cancer (invasive ductal carcinoma) and 30 with benign breast tumor) who attended Kirkuk Oncology Center, Azadi Teaching Hospital, and Kirkuk General Hospital during the period from March/2021 to December/2021 for diagnostic or surgical operations without any prior history of receiving...
radiotherapy and chemotherapy, and 30 apparently healthy women with an age range from 22-56 years were chosen as a control group. The clinico-pathological characteristics were collected and included tumor grade, histology, regional lymph node involvement, hormone receptor status, and HER2 status. All study participants signed a written informed approval form for sample collection and utilizing of their medical register for study objectives. Exclusion criteria for enrolment in the study group were pregnant females and patients with clinical or pathological evidence of any other carcinomatous disease history of cancer at any other site or of having received any type of neoadjuvant therapy.

Venous blood samples were also taken from each subject in this study before surgery and treatment. Centrifugation was used to obtain serum samples and immediately stored at -20 C until testing. Preoperative serum level of CA15-3 level was determined using an Enzyme-linked immunoabsorbent assay (ELISA) technique (Sun long/ china) by the manufacturer's protocol. The Immunohistochemistry (IHC) method was utilized to determine the expression of estrogen receptor (ER), progesterone receptor (PR), and HER-2. The presence of more than 10% nuclear-stained cells was classed as ER-positive and PR-positive. While, positive results of HER2 were pointed by a 3+ or 2+ score from the immunohistochemical estimation.

2.2. Statistical analysis

Statistical Package for Social Sciences version (SPSS) version 26.00 was utilized for all data analysis. The data are expressed as means ± standard deviation and median. Variations between study groups were determined by One-way analysis of variance (ANOVA) (Fisher’s exact probability test) while the chi-square test was used to analyze the association of clinicopathological factors. Statistically significant was defined by P values less than 0.05. Receiver operating characteristic curve (ROC) analysis was used to estimate the diagnostic precision.

3. Results

This study was carried out on 60 patients with breast tumor (30 with primary breast cancer and 30 with benign breast tumor) and 30 healthy control individuals. The preoperative serum levels of CA15-3 in study groups are illustrated in Fig. 1. Determination of CA15-3 level showed significant difference between its level of the sera of primary breast cancer (50.00± 48.22 U/ml) in comparison to the benign breast tumor (19.28± 6.57 U/ml) (p <0.001) and healthy control women one (15.11± 1.39U/ml) (p <0.001).

![Fig 1. The serum level of the CA15-3 among study groups](image-url)
Receiver operating characteristic curve (ROC) analyses were utilized to assess the diagnostic precision of CA15-3 for breast cancer. The area under the curve (AUC) of CA15-3 for differentiating women with primary breast cancer and women with benign breast tumor was 0.532 (95% CI: 0.398 to 0.662). While the AUC of CA15-3 for differentiating women with primary breast cancer and healthy control subjects was 0.720 (95% CI: 0.589 to 0.828). The cut-off value of CA15-3 for differentiating women with primary breast cancer from subjects with benign breast tumor was (>35.92), furthermore, for differentiating women with primary breast cancer from healthy control women was (>16.13). In addition, the Sensitivity and Specificity of CA15-3 for differentiating women with primary breast cancer and women with benign breast tumor were 36.67% and 100% respectively. While, differentiating women with primary breast cancer from healthy subjects was 46.67 and 96.67% respectively, as shown in Fig. 2.

The association between serum CA15-3 level and the clinico-pathological features among patients with breast cancer was listed in Table 1. It is clear from this table that the level of CA15-3 was correlated with the size of the tumor. Patients with tumor size (≥3cm) had significant elevation in CA15-3 level than patients with tumor size (<3cm) (p =0.005). As to lymph node status, CA15-3 values were significantly elevated in patients with metastasis of lymph node than in patients without metastasis (p <0.001). This table also revealed that there was no significant association in the CA15-3 level based on age, family history, menopausal status, histologic grade, and (ER, PR, Her2) expression.

![Fig 2. The ROC curve plot of CA-15–3, (A) for differentiating women with breast cancer and women with benign breast tumor; (B) for differentiating women with breast cancer and healthy control subjects](image)

<table>
<thead>
<tr>
<th>Clinico-pathological characteristics of BC patients (N=30)</th>
<th>Variable</th>
<th>No (%)</th>
<th>CA15-3 (U/ml) Median (25%-75%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(Years)</td>
<td>&lt;45</td>
<td>12 (40.00)</td>
<td>15.97 (15.92-20.64)</td>
<td>0.083</td>
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<td></td>
<td>≥45</td>
<td>18 (60.00)</td>
<td>27.52 (15.88-123.80)</td>
<td></td>
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<tr>
<td>Family history</td>
<td>Yes</td>
<td>13 (43.33)</td>
<td>15.95 (15.85-75.23)</td>
<td>0.996</td>
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<tr>
<td></td>
<td>No</td>
<td>17 (56.67)</td>
<td>18.88 (15.95-55.24)</td>
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<td>Menopausal status</td>
<td>Pre-</td>
<td>17 (43.33)</td>
<td>16.02 (15.95-36.16)</td>
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<td>Post-</td>
<td>13 (56.67)</td>
<td>18.88 (15.85-92.24)</td>
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<td>Histologic grade</td>
<td>I</td>
<td>2 (6.67)</td>
<td>14.61 (12.92-16.30)</td>
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<tr>
<td></td>
<td>II</td>
<td>16 (53.33)</td>
<td>16.02 (15.95-113.62)</td>
<td>0.48</td>
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<td>III</td>
<td>12 (40.00)</td>
<td>26.06 (15.87-65.24)</td>
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<tr>
<td>Tumor size</td>
<td>&lt;3</td>
<td>18 (60.00)</td>
<td>15.97 (15.89-16.23)</td>
<td>0.005*</td>
</tr>
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<td></td>
<td>≥3</td>
<td>12 (40.00)</td>
<td>83.74 (31.09-137.9)</td>
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<td>Lymph node metastasis</td>
<td>Negative</td>
<td>9 (30.00)</td>
<td>15.95 (15.85-15.98)</td>
<td>&lt;.001*</td>
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<td></td>
<td>Positive</td>
<td>21 (70.00)</td>
<td>36.16 (15.95-123.80)</td>
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<td>ES status</td>
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<td>9 (30.00)</td>
<td>18.88 (15.95-55.24)</td>
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<td>Positive</td>
<td>21 (70.00)</td>
<td>16.02 (15.88-92.24)</td>
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<tr>
<td>PR status</td>
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<td>14 (46.67)</td>
<td>27.52 (15.95-75.23)</td>
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<td>Positive</td>
<td>16 (53.33)</td>
<td>15.98 (15.87-74.39)</td>
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<tr>
<td>HER-2 status</td>
<td>Negative</td>
<td>20 (66.67)</td>
<td>16.16 (15.92-65.24)</td>
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<td>Positive</td>
<td>10 (33.33)</td>
<td>16.00 (15.88-146.60)</td>
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</table>

CA15-3 = cancer antigen15-3; ER = estrogen receptor; HER-2 = human epidermal growth factor receptor; PR = progesterone receptor;

* = P < 0.05 means a significant difference
4. Discussion

Despite the incidence ratio of breast cancer has been rising, the death-ratio has stayed steady for decades. This is especially attributed to the early detection and the successful checking programs, in addition to progress in therapy [11]. Cancer antigen 15-3 (CA15-3) is the most frequently utilized as a tumor marker in the clinical practice for the administration of breast cancer. It is evolved as a noninvasive, facely obtainable, and low-cost tumor marker for direct detection, surveillance of therapy response, and breast cancer prognosis [12, 13]. However, the predictive efficiency of preoperative elevation of CA15-3 levels in breast cancer stays argumentative. The finding of the current study referred to significantly elevated preoperative CA15-3 level in primary breast cancer patients than in benign breast tumor and healthy control women, which were in agreement with the study of Lian et al. [14]. In addition, studies by Lee et al. showed that patients with higher CA15-3 levels before surgery also revealed a higher level of CA15-3 at the recurrence of tumor. [15]. Elevated CA153 was observed in breast cancer. ROC analyses were used to analyze the diagnostic precision and revealed that CA15-3 had less diagnostic precision (AUC ≤ 0.700) for differentiating women with primary breast cancer from healthy control subjects, besides differentiating women with primary breast cancer from women with benign breast tumor. Thus, the current study concludes that CA15-3 had less diagnostic precision for primary breast cancer (grad I-III). The CA15-3 cut-off values in three groups showed that they have low sensitivity and high specificity for identifying primary breast cancer. From this viewpoint, the low sensitivity restricted their use for screening breast cancer in an early stage whereas the high specificity referred that positive results should be given special attention. Furthermore, reliable prediction factor must be considered to guide decision-making and proper therapy [16]. Currently, the most widely used pathological characteristics for breast cancer are the age of the patient, size of tumor, the status of lymph node, receptor of the hormone and human epidermal growth factor receptor 2 (HER2) [17].

The current study revealed the relationship between abnormal preoperative CA15-3 level and tumor extent in primary breast cancer women, with significantly higher levels in patients with greater size tumors and lymph nodal invasion. However, no correlation was seen between preoperative CA15-3 levels and (ER, PR, HER2) expression. These outcomes are consistent with the findings of the majority of previous studies [15, 18, 19], which found that CA15-3 values are linked to tumor burden index such as size of tumor and lymph nodal invasion but not to ER or PR expressions. Recently, Zhao et al. [20] studied the relationship between CA15-3 and most essential clinico-pathological characteristics in 961 patients with breast cancer. Patients having greater size of tumor (p < 0.0001) along with nodal metastasis (p = 0.0001) revealed higher rates of elevated CA15-3 levels, similar to our results. Mudduwa et al. [21] identified a significant association only between elevated preoperative CA15-3 and tumor size. However, overexpression of ER, PR, and HER2 did not exhibit a significant correlation with preoperative CA15-3 levels. Other studies reported that the values of CA15-3 were strongly correlated with the advanced stages of cancer [22, 23].

A retrospective study, in which the relationship between CA15-3 level and clinico-pathological features was assessed, revealed that elevated CA15-3 was correlated with aggressive features such as higher grades and advanced stage. Furthermore, there was a considerable difference in ER and PR negativity and HER2 positivity according to subtype [24]. A study among young patients recognized that CA15-3 was only significantly associated with TNM stage and tumor size [25]. When considering that tumor markers indicate the number of cancer cells and also their reach to the blood stream, where the marker is assessed, the association between tumor markers and size of tumor or lymph nodal invasion appears rational [26].

The outcomes of the current study are unlike Uygur et al. study [27], which reported no correlation between CA 15-3 levels and nodal involvement. CA 15-3 levels were elevated in HER2 negative individuals. In addition, CA 15-3 levels in metastatic individuals were significantly elevated. In addition, the results of another study [28] showed that non-significant elevated CA15-3 levels were evaluated according to patients’ age, histological kinds, tumor volume, grade, stage, nodal status, and ER and/or PR status. Discrepancies between studies could be attributed to the heterogeneity of the studied populations, sample size, diagnostic techniques, and cutoff values used for tumor marker. The clinical significance of the earlier diagnosis of primary and recurring breast cancer is significant in guiding decision-making for breast cancer therapy to ameliorate survival proportion [29].

5. Conclusion

Collectively, the CA15-3 level of the current study was observed to be higher in breast cancer patients with larger tumors and lymph node metastasis. This implies that a higher level of CA15-3 is correlated to an increased tumor burden.

Acknowledgement

We would like to thank the administration of Kirkuk Oncology Center, Azadi Teaching Hospital, and Kirkuk General Hospital for their assistance in completing this study, as well as all of the volunteer participants who graciously donated their blood samples.

Ethical Approval

Ethical approval for this study was granted from the ethical committee of the Iraqi Ministry of Health (no. 12601).
Reference


