



Article

Biomarkers Expression in Women with Infiltrating Ductal Carcinoma Breast Cancer

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Abstract: Background breast cancer is a heterogeneous, challenging disease. It is the most frequent cancer found in women in the Middle East. Objective to identify women who are at high risk for breast cancer and find the relationship between breast cancer development and breast cancer markers. This helps provide insight into some breast cancer screening tests and make some suggestions about such tests. Methods: 79 women with breast cancer and 79 controls were included in this study. All patients and control serum samples were subjected to determination CA15-3. Tissue samples were collected as FFPE blocks, and all tissue samples were tested to evaluate the expression of ER, PR, and HER2/neu. Results: Breast cancer in our study was predominant in the age group of 41-50 years, while the lowest frequency was in the age group of 71-80 years. ROC AUC indicated a significant association between breast cancer and some variables such as residence, delivery method, and family history of breast cancer, relative degree, abortion number, mastectomy site, marital status, family member, child number, and breastfeeding. Both ER and PR (positivity rate and cell numbers) were with significant predictive values with grade I and grade III breast cancer. While HER-2 was with significant predictive value in breast cancer with grade III and grade IV. CA15-3 mean serum level was higher in breast cancer as compared to control group, increasing gradually with cancer grade and higher in women aged <35 years. ER and PR-positive breast cancer were found in 64.6% of cases, with significant differences between grades of breast cancer. While HER2-positive breast cancer was 26.6%. The mean CA15-3 values were significantly higher in ER, PR, and HER2-positive breast cancer. Conclusion: Residence, delivery method, family history of breast cancer, relative degree, abortion number, mastectomy site, marital status, family member and breastfeeding are significant associations with breast cancer in our studied cohort. About 2/3 of breast cancer cases are ER and PR positive and this may influence the therapeutic approach of breast cancer cases. Fortunately, 1/4 of cases are HER2 positive as they are with poor prognosis. ER, PR, HER2, and CA15-3 markers may be important guides in breast cancer therapy.

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1. Introduction

Cancer is currently the second leading cause of death in the world (8.97 million deaths) following ischemic heart disease, but it is predicted that it will exceed this into 2060 18.63 million deaths. Breast cancer is the most frequent cancer in women and the most common cause of cancer death globally [1], yet the incidence and mortality of the disease vary by geographical area [2]. Asia had the highest breast cancer incidence, 45.4%, followed by Europe, North America, Latin America, and Africa. Breast cancer comprised 54.5 percent of all malignancies in Iraqi women in 2020, and it forms the most frequent cancer in women, followed by thyroid cancer. Breast cancer is the most frequent cancer in Turkish women, accounting for 46.6 percent of all malignancies in women, followed by thyroid cancer [3]. The three most dangerous cancers in the general population are lung,

liver, and stomach cancers, whereas lung and breast cancers are the leading causes of cancer-related death in men and women, respectively [4]. The human epidermal growth factor receptor 2 (HER2), the estrogen and progesterone receptors, are some of the biological characteristics that make breast cancer a diverse disease and clinically used to predict biological subtypes and predict outcome [5]. Breast cancer molecular subgroups differ in preoperative CA15-3 and CEA levels, which provide good predictive indications in women with breast cancer [6].

Serum tumor markers are widely utilized as non-invasive methods for early detecting recurrence, assessing therapy response, and predicting cancer prognosis. Cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA) is the most often utilized serum tumor markers in breast cancer. While CA 15-3 and CEA are not presently approved as markers for breast cancer screening or therapeutic response monitoring by the American Society of Clinical Oncology, they are the most extensively utilized markers in clinical practice for surveillance and therapy response management [7].

CA15-3 is one of the soluble forms of MUC1, a transmembrane protein with varying quantities of tandem repetitions of glycosylated peptides and the well-investigated circulating biomarker for breast cancer [8]. MUC1 is found in the apical membrane of normal secretory epithelial cells and protects the underlying epithelia in healthy tissues, maintaining homeostasis and encouraging cell survival in a variety of situations [9]. MUC1 linked with tumors, on the other hand, contributes to intracellular signal transduction pathways and affects the transcription and posttranscriptional expression of its target genes [8].

The majority of tumor markers are utilized for early diagnosis, prognosis, therapeutic effectiveness monitoring, and post-treatment follow-up [10], [11]. Previous studies in Iraq showed an increased level of CA15-3 in breast cancer patients and that this increase is associated with advanced stages [12]. In another study in Turkey, the circulating tumor cell count and CA15-3 levels in metastatic breast cancer patients were found to have prognostic values [13]. Steroid receptors (SRs) are ligand-activated transcription factors that belong to the nuclear receptor family. SRs govern a wide range of physiological tasks, including reproduction and development, but they are also implicated in a number of diseases, particularly cancer. Highly regulated cellular responses to steroids include genomic activity (transcriptional regulation) as well as non-genomic activity (direct activation of signaling cascades). Non-genomic signaling in cancer has been intensively explored, primarily in breast cancer for estrogen receptor (ER) and progesterone receptors (PR) and prostate cancer for androgen receptor (AR) [14]. The two most essential hormones in the female body are progesterone and estrogen. Early menarche, late menopause, and postmenopausal obesity all raise estrogen exposure over time. Hormone replacement therapy with estrogen and progesterone raises the risk of most invasive breast cancer in Western women by more than 25% [15]. ER is the most significant member of the nuclear receptor superfamily, controlling the replication or apoptosis of certain populations of breast cancer cells. In breast cancer, the progesterone receptor is an estrogen-regulated protein that participates in predicting the hormone dependence of metastatic breast cancer [16]. In preclinical and clinical contexts, the oncogenic potential of human epidermal growth factor receptor 2 (HER2) has been well demonstrated. HER2 has the greatest catalytic kinase activity of the four HER family proteins and operates as the most active signaling complex of the HER family after dimerization with other HER family members [17]. In cell culture and transgenic animal models, overexpression of the HER2 protein promotes malignant transformation [18]. A tumor's stage and grade may be assessed, and tumors can be classified based on the presence of steroid receptors such as the ER, PR, and HER2. If a tumor lacks any of the three receptors ER-PR-HER, it is referred to as (triple negative) breast cancer [19]. When compared to other breast cancer subtypes, this malignancy is linked to a higher chance of recurrence [20].

2. Materials and Methods

2.1 Study design and patient selection criteria

Sample collection started in November 2020 to September 2021 at the Blood and Tumor Test Center of the Kirkuk Health Department in Iraq, Samples and information collection were approved by the ethical committee stipulated by the Iraqi Ministry of Health (21884 in September 2020). All serum samples were preserved at -20 0C before assay.

1. Study cases: 79 women with breast cancer and 79 controls (apparently healthy woman with matched age group) were included in this study.
2. Exclusion criteria Cases with full clinical details and follow-up were unavailable; those with insufficient representative tissue for immunohistochemistry (IHC).

2.2 Biomarkers detection

All patient and control serum samples were subjected to the determination of CA15-3 and 79 tissue samples collected as FFPE blocks. CA15-3 was detected in patient blood samples using the Cobas e 411 analyzer. For immunoassay analysis, a completely automated analyzer ElectroChemiLuminescence (ECL) technology has been used. Immunohistochemistry –Immunostaining was performed for evaluating the expression of ER, PR, and HER2/neu on tissue sections cut from formalin-fixed, paraffin-embedded (FFPE). Four micrometer-thick sections were deparaffinized with xylene and rehydrated in alcohols that down-regulated. According to the instructions on the (Using Dako cytometry Envision +Dual link system HRP (DAB+) manual sheet, all tissues were prepared and incubated with the appropriate mouse monoclonal anti-human ER, PR, or HER-2/neu primary antibody. Semi-quantitative analysis of ER-stained tissue sections was performed following the Allred scoring system guidelines [21]. ER and PR were considered positive when 10 % or more of the cancer cells stained positively. Our patients were classified as ER positive, P (score 2-8) or negative, N (score 0). PR positive, P (score 2-8) or negative, N (score 0). The UK National External Quality Assessment Scheme for IHC [22], was used to score the HER2/neuimmuno-reaction. This is a semi-quantitative method that uses the strength of cell membrane immunoreaction and the percentage of membrane positive cells to get a score from 0 to +3. Score 0 is assigned when no staining or membrane staining is observed in less than 10% of tumor cells, score +1 when a faint partial membrane staining is observed in more than 10% of tumor cells, score +2 when a weak to moderate complete membrane staining is observed in more than 10% of tumor cells, and score +3 when a strong complete membrane staining is observed in more than 10% of tumor cells. Only values +3 were regarded to be positive for HER-2/neu overexpression, whereas scores 0 and +1 were considered negative.

2.3 Statistical Analysis

The results are expressed by mean $\pm$ SD and frequency. For means between groups, T test and ANOVA were used. Chi square test was used to compare frequency difference between groups P value of <0.05 was considered as significant. Logistic regression line analysis was used to determine odd ratio. Recessive Operative Curve (ROC) was used to find out area under curve (AUC) When the probability was greater than 0.5, the instance has been classified as positive, 0.5 had determined as the decision threshold. IBM SPSS statistics ver.26 and MS excel 2016 were used.

3. Results

Demographic and Epidemiological Characteristics of Woman with Breast Cancer

Seventy-nine women with breast cancer were included in this study in the age range of (20 to 71). The most common cases were in the age group of 41-50 years, while the lowest frequency was in the age group of ≥ 71 years; the frequency distribution of the cases shown in **(Figure 1)**.

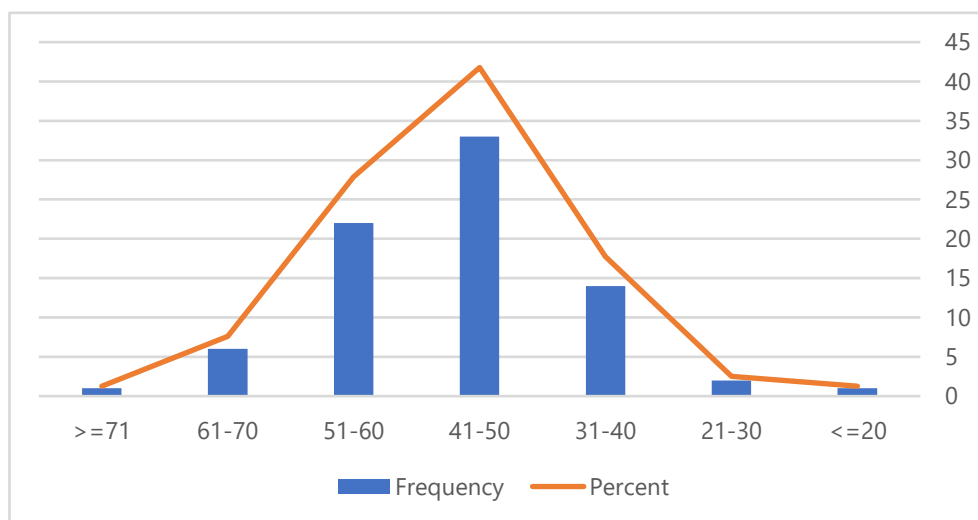


Figure 1. Frequency Distribution of Breast Cancer Cases According to Age

About half of the cases (45.6 %) were in grade two of breast cancer, followed by grade three (31.6%), while the lower rate was in grade four **(Figure 2)**.

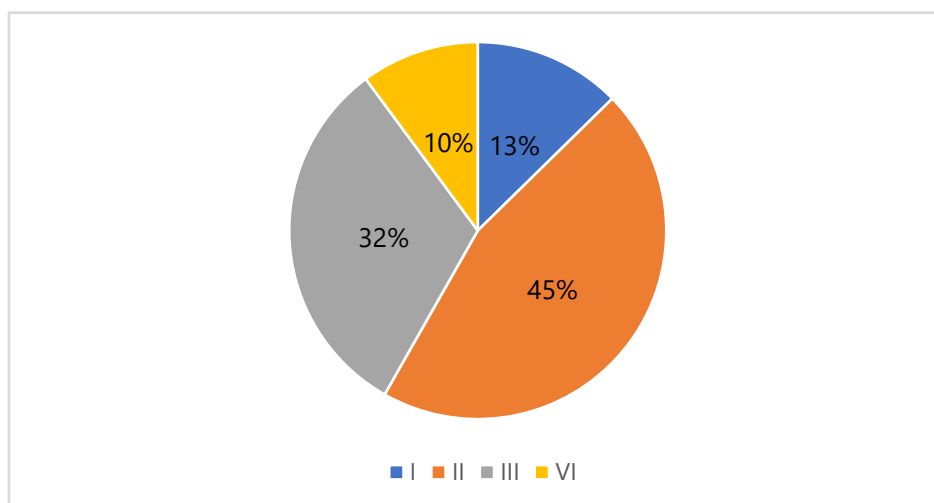


Figure 2. Frequency Distribution of Breast Cancer Cases According to Grade

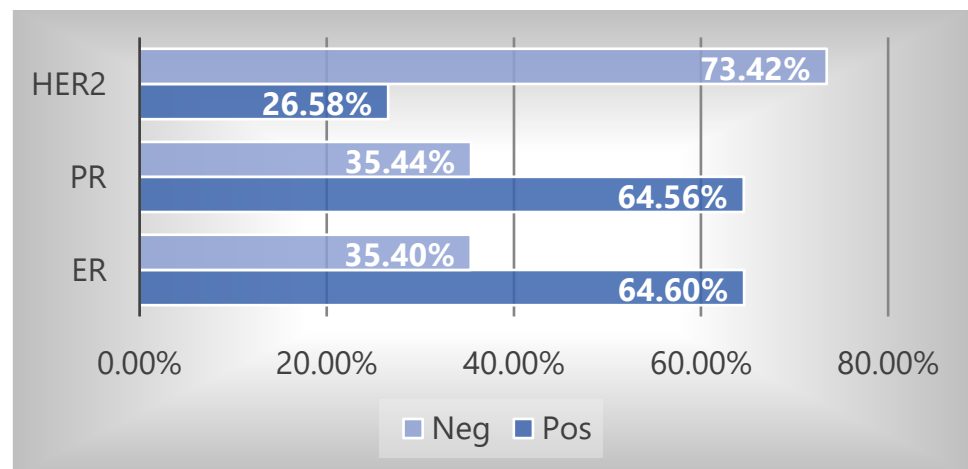
The ROC AUC values indicated a significant association between breast cancer and some variables such as residence (AUC=0.639), delivery methods (AUC=0.609), family history of breast cancer relative degree (AUC=0.585), marital status (AUC=0.558), abortion number (AUC=0.576), mastectomy site (AUC=0.567), marital status (AUC=0.558), family history of breast cancer (AUC=0.533), child number (AUC=0.532), and breastfeeding (AUC=0.502). While blood group, education levels, SES, drug history, and menses irregularity did not show a significant association with breast cancer (ROC AUC < 0.50), as shown in **(Table 1)**.

Table 1. Area under ROC Curve of Demographic, Socioeconomic, Gynecological and Medical History in Woman with Brest Carcinoma

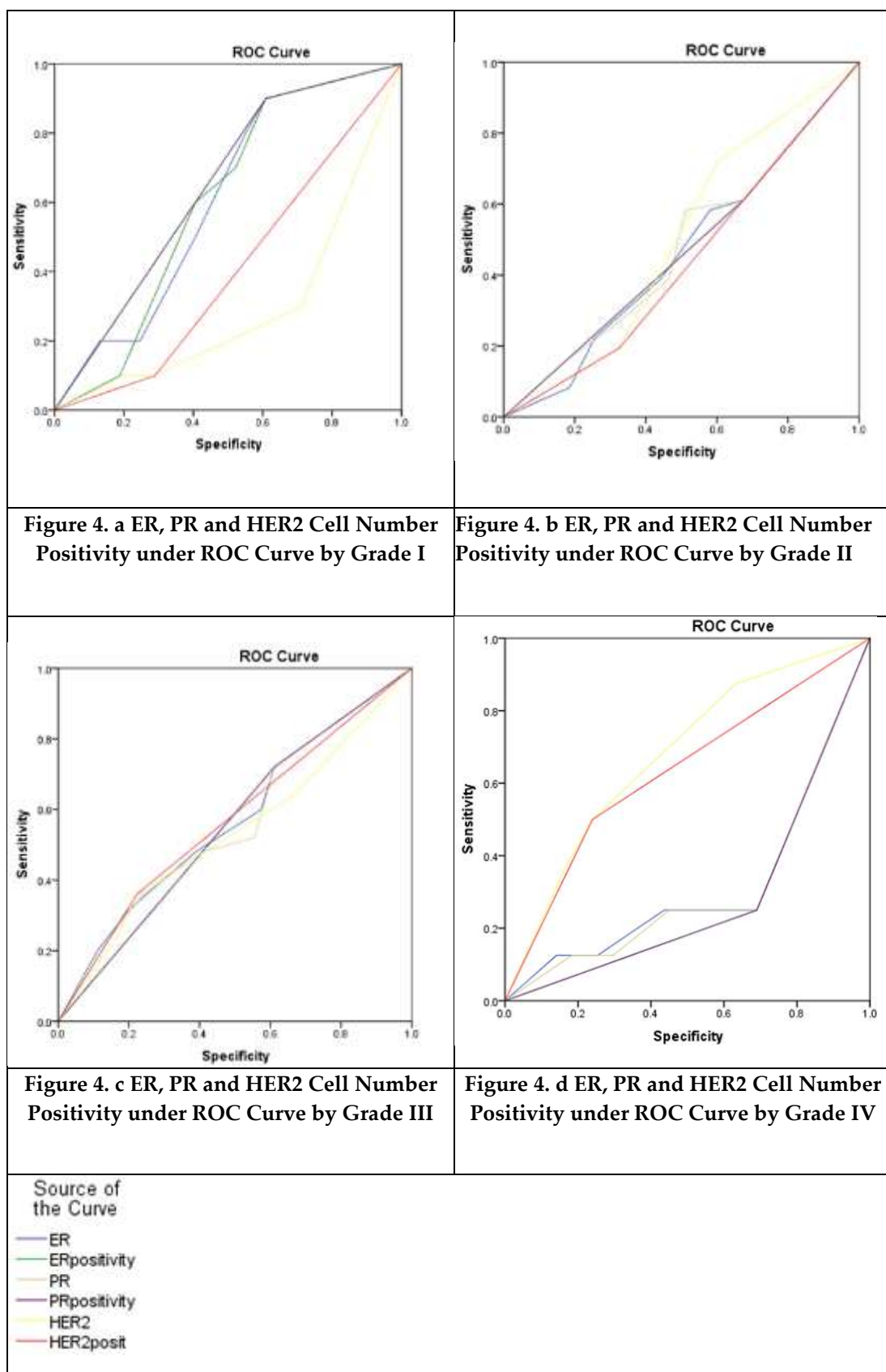
Test Result Variable(s)	AUC
Residence	0.639
Delivery Method	0.609
Family History of Brest Cancer Relative Degree	0.585
Abortion Number	0.576
Mastectomy Site	0.567
Marital Status	0.558
Family Member	0.533
Family History of Brest Cancer	0.533
Child Number	0.532
Breast Feeding	0.502
Drug History	0.497
Menses Irregularity	0.47
Blood Group	0.464
Education	0.464
Socioeconomic Status	0.341

ER, PR & HER2 in Breast Cancer

Our present study showed that 64.56% of breast cancer cases were PR positive. The same pattern of ER positivity. The same ER-PR Positivity pattern, with a lower positivity rate, was observed by [23], the age group 41-50 years had the highest levels of positive ER (23.4 %) and PR (23.4 %). In another study, 84.4 % of breast cancer was PR positive [24].

**Figure 1.** The Mean Value of ER, PR&HER2 in Women with Breast Cancer

About the association of breast cancer grade with ROC AUC, both ER & PR (positivity rate and cell numbers) have significant predictive value with grade I and III breast cancer, as shown in (Figure 4. a), (Figure 4. c). While HER-2 was with significant predictive value in breast cancers with grade III and IV, as shown in (Figure 4.c) (Figure 4.d).



CA15-3 Biomarker in Patient with Breast Cancer

The mean serum level of CA15-3 in patients with breast cancer was significantly ($t=15.03$, $p < 0.001$) higher in patient (226.83 ± 126.47 mg) as compared to control (12.58 ± 7.39) (Table 2).

Table 2. Mean of serum level of CA-15-3 in Patient with Breast Cancer

GROUPE	Number	Mean	Std. Deviation
Control	79	12.58	7.39
Patient	79	226.83	126.47

$t=15.03$; $p<0.001$

Analysis of CA15-3 concerning (35,40,45,50,55) and 60 age strata did not show a significant difference in serum CA15-3, except women with age of <35 years that showed a significant ($P=0.04$) higher mean value in comparison to those with the age group of 35 years & more (Table 3).

Table 3. Mean Serum Level of CA15-3 According to Age Group

Age in year	Number	Mean	Std. Deviation	Std. Error Mean
≥ 35.00	75	225.90	120.68	13.93
<35.00	4	244.32	237.16	118.58

$t=0.28$; $p=0.04$

The mean serum level of CA 15-3 In breast cancer patients was associated with the cancer grade level. The mean value was (57.88 ± 32.97) in a patient with grade 1 and increased to (190.75 ± 75.79), (271.48 ± 73017), and (460.86 ± 112.15) for grades 2, 3&4, respectively (Table 4).

Table 4. Mean of serum level of Breast Cancer Biomarker (CA-15-3) in Relation to Grade

Grade	Number	Mean	Std. Deviation
I	10	57.88	32.97
II	36	190.75	75.79
III	25	271.48	73.17
IV	8	460.86	112.15
Total	79	226.83	126.47

$t=47.99$; $p<0.001$

CA15-3 Marker in Correlation to ER, PR&HER2

CA15-3 mean serum value was significantly ($t=4.69$; $p=0.02$) higher in ER-negative&PR negative breast cancer (268.55 ± 133.06) than in ER-positive cases (203.93 ± 117.83) (Table5).

Table 5. CA15-3 Mean Serum Level in Correlation to ER and PR

ER	Number	Mean	SD.	PR	Number	Mean	SD.
Positivity				Positivity			
Negative	28	268.55	133.06	Negative	28	268.55	133.06
Positive	51	203.93	117.83	Positive	51	203.93	117.83
Total	79	226.83	126.47	Total	79	226.83	126.47

$t=4.69$; $p=0.02$

$t=4.69$; $p=0.02$

The mean serum value of CA15-3 does not show a specific pattern of association with ER-positive cell numbers. Cases with three positive cells were with mean serum value of (225.77±102.62), while in those with four positive cells, the mean serum value was (182.7±104.52) and reduced to (172.25±130.12) in cases with five ER-positive cell cases (**Table 6**).

Table 6. CA15-3 Correlation to ER and PR Cell Number

Cell Number	Number	Mean	SD	PR Cell Number	Number	Mean	SD
0	28	268.55	133.06	0	28	268.55	133.06
3	5	225.77	102.62	3	8	221.47	126.16
4	13	182.70	104.52	4	9	174.10	80.47
5	14	172.25	130.12	5	12	203.32	145.10
6	8	233.76	62.71	6	8	161.79	76.44
7	11	237.72	152.10	7	14	237.68	129.46
Total	79	226.83	126.47	Total	79	226.83	126.47
F=0.517; p>0.05				F=1.498; p>0.05			

In contrast to ER and PR, the HER2 positive breast cancer cells were with significantly (t=4.04; p=0.04) higher correlation with CA15-3 (273.48±126.56) than those were HER2 (209.94±123.19) (**Table 7**).

Table 7. CA15-3 Correlation to HER2 Positivity

HER2 Positivity	Number	Mean	Std. Deviation
Negative	58	209.94	123.19
Positive	21	273.48	126.56
Total	79	226.83	126.47
t=4.042; p=0.04			

In addition, the number of positive HER2 breast cancer cells correlated to the mean values of serum CA15-3. In women with one HER2 positive cell, the mean serum value was (212.71±135.06), which increased to (234.65±99.18) in-group of two cells HER2 positive and to (289.01±135.88) in-group of three HER2 positive breast cancer cells. In other words, the CA15-3 level increased in ascending way with the level of HER2 – overexpression in breast tissue. The positivity frequency increased from six in the two-cell number field to fifteen in the three-cell number field (**Table 8**).

Table 8. CA15-3 Correlation to HER2 Cell Number

Cell Number	Number	Mean	Std. Deviation
0	27	206.77	136.02
1	31	212.71	113.06
2	6	234.65	99.18
3	15	289.01	135.88
Total	79	226.83	126.47
F=1.608; p>0.05			

4. Discussion

The most common cases were in the age group of 41-50 years, while the lowest frequency was in the age group of ≥ 71 years; the frequency distribution of the cases shown in **(Figure 1)**. About half of the cases (45.6 %) were in grade two of breast cancer, followed by grade three (31.6%), while the lower rate was in grade four **(Figure 2)**. The ROC AUC values indicated a significant association between breast cancer and some variables such as residence, delivery methods, family history of breast cancer relative degree, marital status, abortion number, mastectomy site, marital status, family history of breast cancer, child number, and breastfeeding. While blood group, education levels, SES, drug history, and menses irregularity did not show a significant association with breast cancer (ROC AUC < 0.50), as shown in **(Table 1)**. As both a prognostic and predictive marker, ER is essential in the management of breast cancer patients [25]. In the present study, we found that 64.6% of breast cancer were ER-positive, while 35.4% were ER-negative **(Figure 3)**. This finding is closely related to that reported previously in Iraq and Turkey, with an ER positivity rate of 66.2% and 72.5%, respectively [26], [27]. PR is essential in the management of breast cancer patients [25].

HER2- positive breast cancer is an aggressive form of breast cancer with a poor prognosis and low overall survival. It is reported that 15-20% of breast cancer patients are HER2-positive [28]. In our study, the HER2 positive in breast cancer cells rate was 26.58%, while the HER2 negative breast cancer cells rate was 73.42%, a pattern that was not in accordance with that of ER and PR positive breast cells frequency **(Figure 3)**. Our result was similar to that observed by [24], with a 26.3% HER2 positivity rate. While in another study, the positivity rate was lower than 16% [23].

The mean serum level of CA15-3 in patients with breast cancer was significantly ($t=15.03$, $p < 0.001$) higher in patient (226.83 ± 126.47 mg) as compared to control (12.58 ± 7.39) **(Table 2)**. It is in agreement with what has been reported for another geographical region. [29], [26]. In addition, this finding agreed with the result of the different population in another study [30].

Analysis of CA15-3 concerning (35,40,45,50,55) and 60 age strata did not show a significant difference in serum CA15-3, except women with age of <35 years that showed a significant ($P=0.04$) higher mean value in comparison to those with the age group of 35 years & more **(Table 3)**. However, this finding was unmatched with that reported previously in Iraq, with the insignificant association of age <35 with the mean serum level of CA15-3 and a significant difference was observed at age <40 [31]. Our finding is very close to that found elsewhere in the world; when compared to older patients; younger patients had considerably greater CA15-3 levels [32]. In another study outside Iraq, there was a different result, Patients over the age of 60 were displayed a noticeably higher level of CA15-3 as compared to other age groups, demonstrating a strong link between the amount of CA15-3 and patient age ($P < 0.0001$) [33].

ANOVA test indicated a significant difference in CA15-3 mean serum levels among case grades ($t=47.99$; $P < 0.001$) **(Table 4)**. This finding is in agreement with a previous meta-analysis study; which included 31 studies that reported collected data for serum CA15-3 and had cutoff values ranging from 20.11 to 77 U/ml; discovered that increased CA15-3 was correlated to a higher histological grade and a younger age [34]. In another study, patients in stage III of the disease had a strong association between their CA15-3 levels in comparison with those at other stages ($P 0.01$). Still, there was no statistically significant difference between the levels of CA15-3 at the other grades [33]. Unexpectedly [35], found that, CA15-3 showed a strong inverse relationship with tumor grade ($P = 0.03$).

CA15-3 mean serum value was significantly higher in ER-negative & PR negative breast cancer than in ER-positive cases. This finding agreed with that previously reported by [36], where CA15-3 has a negative correlation with ER and PR expression **(Table 5)**.

The mean serum value of CA15-3 does not show a specific pattern of association with ER-positive cell numbers. However, the value increased gradually in those with six and seven ER-positive cells. Demonstrated the same pattern for PR cell positivity; however, the number of PR-positive cancer cells did not show a specific trend of association with mean serum CA15-3 values **(Table 6)**.

In contrast to ER and PR, the HER2 positive breast cancer cells were with significantly higher correlation with than those were HER2 (**Table 7**). Our finding was in line with previously reported [36], [12], Serum CA15-3 levels elevated in patients with HER2 expression in tumor tissue. In another study, the serum level of CA15-3 does not correlate with HER2_neu ($p < 0.15$) [37].

In addition, the number of positive HER2 breast cancer cells correlated to the mean values of serum CA15-3. In other words, the CA15-3 level increased in ascending way with the level of HER2 – overexpression in breast tissue. The positivity frequency increased from six in the two-cell number field to fifteen in the three-cell number field (**Table 8**).

5. Conclusion

In our study, the most common cases of breast cancer were in the age group 41-50 years, while the lowest frequency was in the age group 71-80 years. About half of the cases were in grade II of breast cancer followed by grades III and VI. CA15-3 marker means serum value was significantly higher in breast cancer cases as compared to control and the Serum level was significantly different according to grade, age of the patient. We found in our study that 64.56% of breast cancer cases were ER and PR positive and Ca15-3 has a positive correlation with ER, PR, and HER2.

The area under rock curve (ROC) suggested a significant association with residence, delivery method, and family history of breast cancer relative degree, abortion number, mastectomy site, marital status child number, and breastfeeding. The area under rock curve (ROC) suggested a significant association of both ER and PR cell number positivity rate with grades I and III of breast cancer. As a result of our current study, we recommend that a Large-scale study is warranted. HER2 screening should also be performed routinely as this phenotype are with bad prognosis and low-rate survival. Importantly, establishment of health education program for women from secondary schools for breast cancer risk factors.

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