The role of c-Myc and other cancer metabolism markers in breast cancer with Luminal A and HER2-positive

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Abstract:

Background: Breast cancer, a prevalent malignancy in women, varies biologically across subtypes defined by ER, PR, and HER2. c-Myc, a critical tumor promoter, modulates metabolic pathways that increase glucose uptake, fueling rapid tumor growth and presenting a potential therapeutic target. Moreover, biomarkers such as LDH (cancer metabolism), HbA1c (long-term blood sugar), AST/ALT (liver function and toxicity), CA27-29 (breast cancer-specific marker), and lipid profiles (metabolic alterations) were analyzed.

Objectives: This study aims to investigate the role of c-Myc and metabolic markers, including LDH, HbA1c, ALT, AST, and lipid profile, in cancer metabolism, with a particular focus on the Luminal A and HER2-positive breast cancer subtypes. Furthermore, it explores the significance of CA 27.29 as a potential marker for assessing the progression and aggressiveness of these subtypes of breast cancer.

Materials andMethods: The study involved 80 women (aged 34-58): 22 with Luminal A, 22 with HER2-positive breast cancer, and 36 age-, sex-, and BMI-matched healthy controls. c-Myc levels were measured using ELISA kits.

Results: c-Myc levels were significantly higher in breast cancer patients (4.68±3.59 ng/ml) than controls (0.83±0.50 ng/ml). CA 27-29 levels were also elevated. Metabolic parameters, including LDH, HbA1c%, ALT, AST, and lipid profiles (except HDL), showed significant changes, with lower HDL in cancer patients. HER2-positive patients had higher CA 27-29 and LDH levels, suggesting greater treatment resistance and disease progression, with no significant differences in other markers.

Conclusion: Monitoring metabolic markers, particularly c-Myc, is essential for understanding cancer metabolism and underscores the need for targeted therapies to enhance prognosis and treatment outcomes, especially in aggressive HER2-positive breast cancers.

Keywords: Breast cancer, c-Myc, Cancer Metabolism, Luminal A, HER2-positive.

1. Introduction

Breast cancer is the most commonly diagnosed type of cancer in women[1].Several risk factors contribute to the development of breast cancer, including age, gender, genetics, lifestyle, and environmental toxins [2]. Key biomarkers such as Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2) play an essential role in the diagnosis and prognosis of the disease, assisting in the assessment of its presence and progression[3].BCa subtypes are classified by immunohistochemistry into luminal A (ER+/PR+/HER2−), luminal B (ER+/PR+/HER2+), HER2-positive (ER−/PR−/HER2+), and triple-negative (ER−/PR−/HER2−)[4]. The luminal A subtype is ER/PR-positive and HER2-negative, whereas the HER2-positive subtype is characterized by HER2 overexpression and the absence of ER and PR receptors[5].Breast cancer cell proliferation, survival, migration, and drug resistance are driven by aerobic glycolysis, or the Warburg Effect, where glucose is converted to lactate via pyruvate and LDH, even with sufficient oxygen. This process bypasses oxidative phosphorylation to produce ATP. Targeting the Warburg Effect and key glycolytic enzymes may inhibit cancer proliferation and invasion, offering potential for glycolysis-based therapies for breast cancer[6].

Cellular Myelocytomatosis Oncogene (c-Myc**)**, gene belongs to the Myc family, located on human chromosome 8, encodes the transcription factor c-Myc, which participates in cell cycle progression, proliferation, apoptosis, and cellular transformation [7]. It plays a key role in tumor metabolic reprogramming by controlling glucose and glutamine uptake, metabolism, and the invasive properties of cancer cells [8].CA 27.29, is a protein antigen containing carbohydrates, also known as Breast Carcinoma-associated antigen, which is released into the bloodstream by breast cancer cells[9]. Normal levels are below 40 U/ml, with higher levels indicating a higher likelihood of breast cancer. Approved by the FDA in 1996, CA 27.29 is commonly used to monitor disease progression in patients with stage II/III breast cancer[10].

Lactate dehydrogenase (LDH, EC 1.1.1.27) is a tetrameric enzyme crucial for anaerobic respiration, composed of two isoforms: LDHA, which converts pyruvate to lactate, and LDHB, which catalyzes the reverse reaction. LDH is often overexpressed in cancer cells, contributing to tumor initiation and progression[11]. In breast cancer, cells shift from oxidative phosphorylation to glycolysis, with LDHA playing a central role in this metabolic reprogramming. This shift supports cancer cell proliferation, enhances drug resistance, and protects cells from apoptosis by mitigating the effects of reactive oxygen species (ROS)[12].

Transaminase enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are essential for amino acid metabolism in liver cells. ALT,

primarily concentrated in the liver, is linked to anaerobic glycolysis, with implications for diseases such as cancer [13].Chemotherapy treats breast cancer by destroying cancer cells but may also harm normal cells and disrupt blood cell production. Routine blood tests, including liver function tests (AST, ALT), monitor the impact on organs like the liver and kidneys. Studies have explored the effects of chemotherapy and metastasis on liver function in breast cancer patients[14]. Additionally, tamoxifen (TAM), an anti-estrogenic treatment, has been associated with elevated levels of both AST and ALT [15].Glycated hemoglobin (HbA1c), the gold standard for glycemic control with a target below 7%, is strongly linked to metabolic syndrome (MetS) components and may predict dysmetabolism[16]. Chosen as the marker for glucose levels in this study, HbA1c provides a stable indicator of long-term glucose control, reflecting average blood glucose over the past 2-3 months[17].

This study aims to investigate the role of c-Myc and metabolic markers, including LDH, HbA1c, ALT, AST, and lipid profile, in cancer metabolism, with a particular focus on the Luminal A and HER2-positive breast cancer subtypes. Furthermore, it explores the significance of CA 27.29 as a potential marker for assessing the progression and aggressiveness of these subtypes of breast cancer.

2. Methods

2.1Study design and sample selection

Blood samples were collected from breast cancer patients at the Tumours Teaching Centre of the Medical City of Baghdad and the Oncology Unit at Al-Yarmook Hospital between August 2023 and January 2024. The study included 80 participants, consisting of 22 individuals diagnosed with Luminal A subtype (ER, PR (+ve), Her2 (-ve)), and 22 with HER2-positive, HR-negative breast cancer. All participants were undergoing a combination of hormone therapy, radiation, and chemotherapy. Additionally, 36 age- and body mass index (BMI)-matched women without breast cancer served as controls. Participants were between the ages of 32 and 58 and had no history of diabetes, polycystic ovary syndrome (PCOS), or other hormonally-related conditions that could influence glucose metabolism. To confirm the diagnosis and evaluate receptor status (HER2, PR, ER), each patient underwent a metastatic biopsy. Anthropometric and biochemical data were gathered using questionnaires. Statistical significance was defined by a p-value of less than 0.05.

2.2 Blood sample collection and outcome measurements

A total of 10 milliliters of venous blood was collected from each participant, including both patients and controls, using a disposable syringe. Of this, 3 milliliters were reserved for HbA1c analysis. The remaining blood was processed by separating the serum into a gel tube, followed by centrifugation at 3000 RPM for 10 minutes at room temperature. The serum was then stored in Eppendorf tubes at -20°C. c-Mycand CA27-29 levels were assessed using ELISA kits (ELK3329 Human Myc BP and Human Cancer Antigen 27-29). The lipid profile, ALT, AST, and LDH levels were measured using Siemens Healthcare equipment, while HbA1c was quantified by Siemens Healthineers.

2.3 Statistical analysis

Data analysis was performed using SPSS version 26, with results presented as mean ± SE. Statistical tests included ANOVA for differences between three independent variables, LSD, T-test, and ROC curve analysis. Linear regression was used for estimation. Statistical significance was set at $p \leq 0.05$, with $p > 0.05$ considered nonsignificant.

3. Results

Demographic Characteristics: Table 1 presents the demographic characteristics of the female participants, including age distribution and mean BMI values for all groups, which were matched for age and BMI.

Type of tumor: Breast cancer patients were classified into two groups based on molecular subtypes: HR (+ve), Her2 (-ve)(Luminal A) and HR-negative, Her2 (+ve)(Her2-positive). Notably, 45% of the breast cancer patients had a family history of the disease.

Disease Duration: The duration of breast cancer in women in this study varied, as the study included those who had been affected for less than a year, those who had been affected for between one and three years, and those who had been infected for more than three years. The duration of the disease depended on several factors, such as the type of cancer (there are many types, each with its own characteristics and speed of spread), the stage of discovery (the earlier the disease is discovered, the better the chances of recovery), the treatment followed (Among the treatments taken for the patients in this study, are tamoxifen, Perjeta (pertuzumab), In addition to chemotherapy, radiation and hormonal therapy), the body's response to treatment, in addition to age and general health of the body, which varies the body's response to treatment.

Table (1): Demographic date of patients and control.

Parameter	Control(n=36)	Patients(n=44)
Number	36	44
Age (year)	50.0±8.17	51.41±9.22
BMI (kg.m2)	26. 97±3.53	27.67±3.84
Duration of the disease		
<1 year	16 (36.36%)	
1-3 years	20 (45.45%)	
>3 years	8 (18.8%)	
Type of tumor		
ER, PR +ve; Her2 –ve (Luminal A)	22 (50%)	
ER, PR -ve; Her2 +ve (Her2-positive)	22 (50%)	
Family history	20 (45%)	

Biomarkers in Control and Breast Cancer Patients for Two Subtypes: Table 2 presents various biomarkers—CA 27-29, c-Myc, HbA1c, LDH, ALT, AST, and lipid profile markers—that provide valuable insights into glucose metabolism, liver function, and lipid profile in breast cancer patients. These markers play a crucial role in assessing patient health, monitoring disease progression, and guiding treatment decisions. The table compares the control group with two distinct tumor subtypes: Luminal A and Her2-positive, with statistically significant differences between the two groups ($p \leq 0.05$) for several biomarkers.

Table 2 : Parameters in Control and Breast Cancer Patients for Two Subtypes

Parameter	Control Group (Mean ± SE)	Breast Cancer Patients (Mean ± SE)	*p*-value	Subtype 1 Luminal A (Mean ± SE)	Subtype 2 Her2-positive (Mean ± SE)	*p*-value
CA27-29 (U/mL)	0.896±0.304	1.788±0.59	0.0001	1.43±0.36^	1.89±0.60^	0.004
c-Myc (ng/ml)	0.83±0.50	4.68±3.59	0.0001	4.88±3.94^	4.04±3.05^	0.43
HbA1c %	3.98±0.58	4.81±0.69	0.0001	5.30±0.71^	5.42±0.74^	0.59
LDH (IU/L)	86.07±18.97	299.17±178	0.0001	243.65±51.99^	366.30±250.04^	0.03
ALT (IU/L)	15.01±7.02	21.64±8.00	0.0001	22.65±7.66^	23.65±9.71^	0.70
AST (IU/L)	13.87±3.90	20.87±7.17	0.0001	19.25±6.73^	22.70±7.91^	0.13
TC (mg/dL)	159.2±20.03	169.98±23.	0.0001	179.15±35.47^	165.65±14.75^	0.10
TGs (md/d	100.9±22.18	119.98±32.	0.0001	121.00±42.38^	115.45±19.70^	0.58
HDL-C (mg/dL)	54.28±5.99	51.02± 8.4	0.048	52.20±8.30^	51.05±8.41^	0.65
VLDL-C (mg/dL)	21.22±4.18	23.90± 6.5	0.0001	24.20±8.48^	23.09±3.94^	0.58
LDL-C (mg/dL)	88.16±16.22	98.29± 26.	0.039	102.75±34.66^	91.51±18.25^	0.19

^ significant corresponding to control.
p ≤ 0.05 indicates statistically significant differences between the control and breast cancer patient groups.
Subtype 1 Luminal A (HR (+ve), Her2 (-ve)) and Subtype 2 Her2-positive (HR (-ve), Her2 (+ve)) represent different molecular subtypes of breast cancer.

CA 27-29 (U/mL): The mean level of CA 27-29 was significantly higher in breast cancer patients (1.788 ± 0.591) compared to controls (0.896 ± 0.304), with a p-value of 0.0001. The levels in the Luminal A subtype were 1.43 ± 0.36, and in the Her2-positive subtype

they were 1.89 ± 0.60, with a significant difference observed between the subtypes (p = 0.004).

c-Myc (ng/ml): On the other hand, c-Myc showed a significant difference ($p \leq 0.05$) between the control and breast cancer patient groups, with values of (0.83 ± 0.50) for controls and (4.68 ± 3.59) for patients, respectively.

HbA1c %: Hemoglobin A1c (HbA1c) was chosen as a stable indicator of long-term glucose control, as demonstrated by Jing Xie et al. [17]. The cumulative HbA1c analysis revealed a significant difference ($p \leq 0.05$), with higher glucose levels in women with breast cancer (who do not have diabetes) compared to the control group. The results were as follows: control group (3.98 ± 0.58) and patient group (4.81 ± 0.69).

LDH (IU/L): The analysis of LDH levels revealed a significant difference ($p \leq 0.05$) between the control group and patients with different types of breast cancer. The control group had a mean LDH level of 86.07±18.97, while patients with breast cancer had significantly higher LDH levels, with a mean of 299.17±170.38.

ALT,AST(IU/L): The activity of ALT and AST in breast cancer patients showed a significant difference ($p \leq 0.05$) when compared to the control group, with all patients undergoing treatment.

Lipid profile (md/dL): This study found a significant decrease in high-density lipoprotein (HDL) levels in the breast cancer patient group, along with an increase in triglycerides (TG), cholesterol, low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) levels compared to the healthy control group, as shown in Table 2. Notably, none of the patients in this study were obese.

Subtypes Results: No statistical differences were observed between the tumor groups for all the studied markers, except for CA 27-29 and LDH, which showed statistically significant differences. Both markers were elevated in Subtype 2 Her2-positive group compared to Subtype 1 Luminal A group.

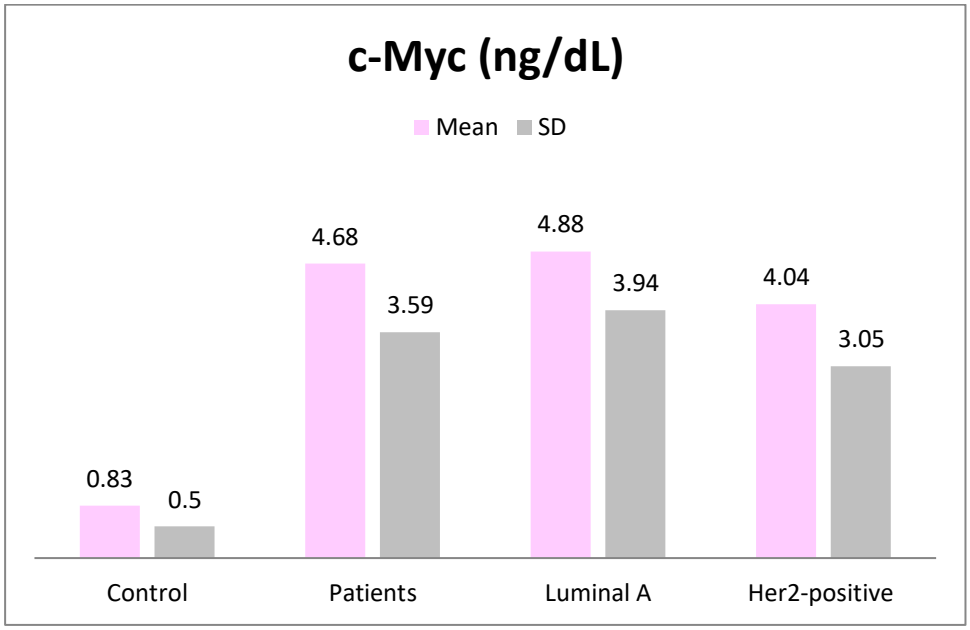


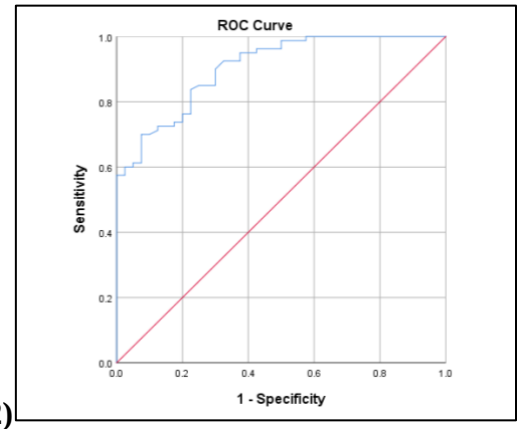
Figure 1: c-Myc expression levels in control subjects and breast cancer patients according to tumor type.

ROC curve parameters: Table 3 and Figures 2 and 3 present the results of the ROC curve analysis for the two biomarkers, CA 27-29 and c-Myc. The analysis includes the AUC, standard error (SE), p-value, cut-off values, as well as the sensitivity and specificity for both study groups of breast cancer patients.

Table 3: ROC curve parameters.

Biomarker	AUC	SE	*p*-value	Cut-off value	Sensitivity	Specificity
CA27-29	0.905	0.026	0.0001	1.22	83.8%	77.5%
C-MYC	0.969	0.013	0.0001	1.33	91.3%	90%

(2)



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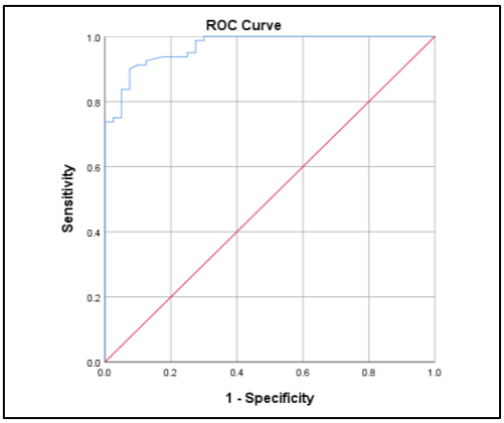

Fig. 2: ROC curve of CA27-29 in the prognosis of breast cancer.

Fig. 3: ROC curve of c-Mycin the prognosis of breast cancer.

4. Discussion

The study included 36 healthy controls and 44 breast cancer patients, ensuring a reasonable comparison between the two groups and enabling robust analysis of health markers and indicators.Minimal differences in age and average BMI between the control and patient groups suggest that these factors do not confound the results, allowing for an unbiased comparison.Most patients (45.45%) were diagnosed 1-3 years ago, reflecting early-stage disease. The 36.36% of patients diagnosed within a year may offer insights into early detection, while the 18.8% diagnosed for over three years represent more advanced or recurrent cases, providing perspectives on long-term survival and disease progression. This diversity in disease duration enhances the exploration of biomarkers at different stages of cancer.The study equally represented two major breast cancer subtypes, facilitating a comprehensive comparison of biomarkers across molecular subtypes and their relationship with breast cancer progression and prognosis.In this study, 45% of patients reported a positive family history of breast cancer, consistent with Rawaa Abdel Amir et al.'s finding of 43.3% [18]. This contrasts with Sergiusz Łukasiewicz et al.'s study, which found that only 13–19% of breast cancer patients had a first-degree relative with cancer [19].

Table (2) highlights significant differences between the patient and control groups, with breast cancer patients exhibiting statistically higher values for several biomarkers ($p < 0.05$). For instance, the mean value of CA 27-29 was significantly elevated in the patient group compared to the control group. These findings are consistent with the research by Shreya Desai et al., who demonstrated that elevated levels of CA 27-29 (>38 U/mL) are strongly associated with breast cancer and are commonly used in its monitoring and surveillance [20]. Moreover, our results align with those of Mahdi Sadeghi et al., who found that higher CA 27-29 levels correlate with more advanced stages of breast cancer and larger tumor burdens, with the highest levels typically observed in cases with metastasis to the bone or liver [21].

On the other hand, c-Myc showed a significant difference $p \leq 0.05$ between control and breast cancer patient groups. Our findings are consistent with those of Fang Yan Gao et al., who highlighted the close relationship between tumor growth and c-Myc expression [7]. Furthermore, c-Myc dysfunction has been shown to regulate cancer stemness and contribute to the reprogramming of cellular metabolism and molecular pathways, as explained by Runtian Wang et al. in their study [22].

This study also contributes to shedding light on the relationship between breast cancer and metabolic and functional changes, which may help improve care and treatment strategies, and provide a deeper understanding of the biological processes associated with

the disease. On this basis, cumulative sugar levels HbA1C and the levels of lactate dehydrogenase (LDH), ALT (alanine aminotransferase), and AST (aspartate aminotransferase) were measured in samples of breast cancer patients, and compared with a group of healthy people. The results showed significant statistical differences between the two groups, reflecting the negative effects of the disease on general health standards.

The elevated HbA1c levels observed in breast cancer patients in our study support the association between increased HbA1c and heightened glucose uptake in cancer cells, which is a hallmark of metabolic reprogramming in breast cancer, as highlighted by Oliver Abrahamsen et al. [23]. Moreover, certain breast cancer treatments, including corticosteroids and chemotherapy, are known to elevate blood glucose levels. This finding is in accordance with the research of Naoko Terao et al., which emphasized that hyperglycemia can be a side effect of steroid use during chemotherapy[24].

The elevated LDH levels observed in breast cancer patients may indicate increased metabolic activity of cancer cells, reflecting their rapid growth and division. This finding is consistent with the study by Petya Apostolova et al., which suggested that tumor cells with high aerobic glycolysis generate lactate through lactate dehydrogenase (LDH) activity [25]. Elevated LDH levels may also be associated with the metabolic changes cancer cells undergo to sustain their rapid proliferation.Gloria KARYEE et al. reported increased LDH activity in cancer patients, attributed to tumor necrosis and possible hemolysis, although their study did not establish a direct link between serum LDH levels and pathological outcomes or anthropometric measurements, highlighting the widespread use of LDH measurement for malignancy detection and evaluating cancer therapy efficacy [12].

These elevated ALT and AST levels could reflect liver involvement or the metabolic changes associated with the progression of breast cancer. The elevated ALT levels observed in breast cancer patients may indicate malignancy and could potentially serve as a marker for predicting breast cancer, in accordance with the findings of Nabaa Haider et al. . However, their study found no significant difference in AST levels [13]. contrary to these findings, Abu Bakr Hamid Ali et al. suggested that liver function tests, including ALT and AST, may not be reliable biomarkers for diagnosing or monitoring breast cancer. Their study found no significant differences between the outcomes of patients and the control group in liver function tests, which raises concerns about the sensitivity and specificity of these tests as diagnostic tools for breast cancer [14].

These findings highlight the potential link between breast cancer and lipid profiles. The decrease in HDL levels in the patient group suggests a possible alteration in lipid metabolism associated with the disease. This is consistent with the study by Ahmad et al., which reported lower HDL and higher triglycerides (TG), low-density lipoprotein (LDL), ALT, AST, and cholesterol levels in breast cancer patients [26].Furthermore,

chemotherapy may affect metabolism and impair fat processing. Aiying Qi et al. found that chemotherapy leads to metabolic disorders, including elevated triglycerides and lowered HDL, while total cholesterol and LDL levels remain unchanged before and after treatment [27].

The observed increase in CA 27-29 and LDH levels in subtype 2; HER2-positive group may reflect the higher aggressiveness or progression of the disease in these patients. As noted by Maria Mercogliano et al. found that HER2-positive breast cancer is one of the most aggressive subtypes, with the poorest survival rates, and resistance to trastuzumab significantly reduces its clinical effectiveness [28].In contrast, the prognosis for the Luminal A subtype is more favorable due to positive responses to hormonal therapies, as noted by G. Dimitrov et al.[29].However, no research has yet confirmed a direct association between the CA 27-29 and LDH markers and the molecular subtypes of breast cancer, as subtype determination cannot be based solely on marker levels.

Based on the ROC analysis (Table 3), both c-Myc and CA 27-29 demonstrate excellent discrimination ability for breast cancer detection, distinguishing between patients and healthy individuals. While c-Myc showed superior performance with a sensitivity of 91.3% and specificity of 90%, both biomarkers are promising tools for monitoring patients and guiding treatment. As shown in Table 3 and Figures 1 and 2, both biomarkers yielded statistically significant results (p-value ≤ 0.0001), indicating a strong association with breast cancer diagnosis and underscoring their reliability and relevance in clinical settings.

5. Conciusion

In conclusion, this study emphasizes the crucial role of c-Myc in the metabolic processes of Luminal A and HER2-positive breast cancer subtypes, particularly its influence on glucose metabolism and tumor growth. The findings highlight the potential of c-Myc and other metabolic markers, such as LDH and CA 27-29, for improving breast cancer diagnosis, treatment, and prognosis. The results align with previous research showing c-Myc's involvement in cancer metabolism, promoting tumor growth, and contributing to drug resistance. Additionally, CA 27-29 serves as a sensitive marker for monitoring disease progression, especially in cases with treatment resistance.

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Ethical Approval

Ethical approval for the study was granted by the Consultancy of the Scientific Board in the Chemistry Department at the Women's College of Science, University of Baghdad. According to the cod number 4846/22, on August 31, 2023.

Authors' Declaration

The author hereby declares that there are no conflicts of interest. We affirm that we hold ownership of all tables presented in this publication. Additionally, permission has been obtained for the republication of statistical data included in this paper, which is not originally ours.

Authors' Contributions

All authors contributed equally to the literature review and the writing of the manuscript. Each author reviewed and approved the final version of the manuscript.

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