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Predictive Power of Multiplex Serum Biomarkers in Breast Cancer: A Comprehensive ROC Curve Analysis

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Abstract

Introduction: Breast carcinoma is one of the most prevalent cancers in women, with its progression influenced by a complex interplay of genetic and environmental factors. This study aimed to investigate the association between resistin, mammaglobin, MUC1, CA153-, CEA, and AKT pathway activation in breast cancer development. Methods: A cross-sectional study design was performed in Iraq/ Medical City at Baghdad/ Oncology Teaching Hospital. All samples (105 samples of blood) were classified into 3 groups; each one contains 35 samples. Results: A serological analysis was conducted using ELISA to measure serum levels of key biomarkers. Malignant samples exhibited elevated concentrations of mammaglobin (mean: 3.74 ng/ml), resistin (mean: 4.195 ng/ml), CA153- (mean: 36.15 ng/ml), CEA (mean: 41.983 ng/ml), mucin1 (mean: 33.45 ng/ml), and AKT (mean: 3.174 ng/ml). Conclusion: The findings suggest that a combined assessment of these tumor markers could enhance the prognosis, diagnosis, detection, and monitoring of breast cancer. Notably, CEA and MUC1 demonstrated superior sensitivity and specificity, positioning them as highly reliable biomarkers for clinical application.

Keywords
AKT, Breast Cancer, Mammaglobin, Mucin1, Resistin

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Introduction

Breast cancer (BC) is one of the most commonly diagnosed tumors in women, and after lung cancer is considered as the primary cause of mortality. There are several factors that affect the risk of developing including age, gynecological and reproductive characteristics, smoking and physical activities and a positive family history [1-3]. Resistin is a cysteine-rich hormone-like protein (adipokine) encoded by the Resistin (RETN) gene. While it is primarily secreted by fat cells (adipocytes) in rodents, in humans, it is mainly produced by immune cells such as macrophages. There is evidence indicating the up regulation of retn gene in some patients suffering from BC and Poly Cystic Ovarian Syndrome (PCOS) [4].

The mammaglobin gene generates a protein in the same name (h-MAM) that is normally expressed at low levels in breast epithelium and in 80% of the breast carcinoma but it is absent in normal tissues. This elevated expression may be linked with tumor grade and stage, or hormone receptor status. Mammaglobin is a protein known for its high specificity to mammary tissue, with significant over-expression in most mammary carcinomas—including aggressive triple-negative breast cancers (TNBCs). Due to its restricted expression in normal tissues and frequent upregulation in breast malignancies, mammaglobin has emerged as a promising molecular target for breast cancer therapy.[5]. The cancer antigen 15-3 (CA15-3), a member of the mucin-1 (MUC-1) glycoproteins family, is over-expressed in various cancers and is recognized as a valuable tumor marker due to its altered glycosylation [6]. Carcino-Embryonic Antigen (CEA); increased levels of carcino-embryonic antigen (CEA) in the blood a type of cell adhesion molecule are related to tumor metastasis. Monitoring CEA is valuable for assessing a patient's future disease course, detecting disease progression early, and aiding in the selection of appropriate therapeutic strategies for BC, in screening, observing the presence of disease, staging, and choosing treatment regimen of BC [7]. Mucin (MUC); Mucins are large, heavily glycosylated proteins produced by various secretory epithelial cells. MUC also referred to as cluster of differentiation 227 (CD-227), Overexpressed and abnormally glycosylated in human carcinomas contributing to tumor invasion and leading to poor prognosis. Additionally rising levels of mucin-type glycoproteins in the serum are associated with increased tumor invasiveness in human [8]. Protein kinase B (AKT); protein kinase that could be activated by insulin and some growth factors functioning within the PI3 kinase pathway [9]. This study aims to elucidate the potential synergistic role of resistin, mammaglobin, MUC1, and the established tumor markers CA15-3 and CEA in breast cancer pathogenesis, with a specific focus on their relationship to aberrant AKT signaling. Given AKT's central role in promoting oncogenic cell survival through the inhibition of apoptosis.

Material and Methods

Study Design: A cross-sectional study design was performed between March-2020 and September-2023 in Iraq/ Medical City at Baghdad/ Oncology Teaching Hospital. At the study setting breast cancer was diagnosed by the oncologist in the hospital depending on accurate results of mammography, cytology and serology tests.

The study targeted patients with breast cancer attending Oncology Teaching Hospital for diagnosis, therapy and ongoing care. Adult women (>18 years) were included in the study. patients with other severe or chronic diseases and pregnant women were excluded. All patient samples were diagnosed via cytology and histopathological review by an oncologist. Groups were defined as: control, benign (fibroadenoma), and malignant (invasive ductal or lobular carcinoma). Subtypes were based on final histopathology. Tissues were promptly preserved in RNA Later Solution to stabilize nucleic acids. This is an exploratory pilot study with 35 samples per group, acknowledging the lack of prior power calculation as a limitation.

The study variables included the stage and grade of cancer depending on TNM (Tumor, Nodes, and Metastasis) classification system determined by the oncologist, so we could classify the blood samples into 3 groups according to diagnostic results; control, benign and malignant.

Data Sources and Measurements: By the use of a questionnaire data were collected from patients and volunteers regarding any factors which may have effect on study results. For avoidance of bias in sampling, samples were collected randomly depending on the socio-demographic data, level of education, occupation, and family history of breast cancer, clinical characteristics and some other details about duration of breast feeding.

Sample Size: All samples (105 samples of blood) have been collected from patients in Hospital. Samples were classified into 3 groups; each one contains 35 samples. This is an exploratory pilot study with 35 samples per group, acknowledging the lack of prior power calculation as a limitation.

The blood sample was collected (3 ml) in gel tube for centrifugation. Then stored in freezing (-2°C). ELISA test was utilized in this study to measure the concentration of biomarkers in serum samples. In this study, the following ELISA kits (Cusabio, China) were used for biomarker quantification: Human Mammaglobin (Catalog No. CSB-EL020817HU), Human Resistin-A (Catalog No. CSB-E06884h), Human Mammary Carcinoma Marker CA15-3 (Catalog No. CSB-E04772h), AKT (Catalog No. CSB-EL001553HU), MUC1 (Catalog No. CSB-EP015215HU), and Human Carcinoembryonic Antigen (CEA) (Catalog No.CSB-E04767h). All samples were run in duplicate, and the mean values were used for statistical analysis The final results were analyzed by the use of ROC curve.

Statistical Analysis: Statistical analysis was performed using SPSS software, version 28.0 (Released 2021; IBM Corp. USA). Normality was assessed using the Shapiro–Wilk test. Group comparisons were performed using one-way ANOVA followed by Fisher's LSD post-hoc test. Statistical signifi-

cance was set at α = 0.05. ROC analysis was conducted using a non-parametric method, and the AUC with 95% confidence intervals was calculated.

Ethical Approval: Ethical Approval was obtained from the ethical committee in University of Baghdad (Ref: 8021; 3-March-2021).

Results:

Evaluation the Concentrations of Mammaglobin by the use of Enzyme Linked Immuno Sorbent Assay: ELISA test was performed to determine mammaglobin level in serum samples of 35 BC patients, 35 women with benign tumor and 35 healthy women as control using mammaglobin ELISA kit, which was able to detect mammaglobin in a range equal to 0.078 – 20 ng/ml. The findings showed that mammaglobin level was increased in malignant group with mean of (3.74 ng/ml) and (0.618 ng/ml) for benign samples and (0.534 ng/ml) for control group (p<0.01) as showed in (Table 1).

Table 1: The mean of Mammaglobin serum levels in all groups.

Group	Number	Mean ± SD (Mammaglobin)
Control Group	35	0.534±0.20b
Benign Group	35	0.618±0.24b
Malignant Group	35	3.74±2.37a
LSD Value	---	0.739 **
P-Value	---	0.0001
Different letters at the same column Means differed significantly. **(P≤0.01).		

Evaluation the Concentrations of Resistin by ELISA

The findings showed that Resistin level was increased in malignant group with mean of about (4.195 ng/ml) and (1.652 ng/ml) in benign group and (1.475 ng/ml) in apparently healthy control group (p<0.01) as shown in (Table 2).

Table 2: The mean of Resistin levels in serum of all groups.

Group	Number	Mean ±SD of Resistin
Control Group	35	1.475±0.28b
Benign Group	35	1.652±0.20b
Malignant Group	35	4.195±2.67a
LSD Value	--	0.657 **
P-Value	--	0.0001
Different letters at the same column Means differed significantly. **(P≤0.01).		

In this study the concentration of Resistin protein in malignant group ranged between (1.55-14.8) ng/ml while it ranged between (1.348-2.225) ng/ml within benign group and ranged between (0.87-1.992) ng/ml in control group. Obesity considered a cancer risk factor, and in obese patients, the likelihood of developing breast cancer may be related to increased estrogen levels resulting from aromatization in fat tissue.

Evaluation the Concentrations of CA15-3 by ELISA

The findings showed that CA15-3 level was increased in malignant group with mean of about (36.15 ng/ml) and (27.08 ng/ml) for benign group and (14.33 ng/ml) for control group (p<0.01) as shown below in (Table 3).

Table 3: The mean of CA15-3 serum levels in all groups.

Group	Number	Mean ± SD of CA15-3
Control Group	35	14.33 ± 4.13c
Benign Group	35	27.08±9.02b
Malignant Group	35	36.15±11.13a
LSD Value	--	4.083 **
P-Value	--	0.0001

** (P≤0.01).

In current study the CA15-3 protein level in malignant group range is about (27.45- 69.5) ng/ml while it ranged between (11.9- 51.59) ng/ml in benign group and ranged between (8.01- 20.1) ng/ml in control group. Clinical evidence demonstrates that elevated CA15-3 levels are present in most metastatic breast cancer (BC) cases, while only a small subset of early-stage/localized cancer patients show such increases.

Estimation of CEA Levels by ELISA

ELISA test was performed to estimate the carcinoembryonic Antigen (CEA) levels in serum samples of 35 patients, 35 women with benign tumor and 35 control using "CEA ELISA" kit, The findings showed that its levels was increased in malignant group with mean of about (41.983 ng/ml) and (16.442 ng/ml) benign group and (11.367 ng/ml) in control group (p<0.01) as shown below in (Table 4).

Table 4: The mean of CEA serum levels in all groups.

Group	Number	Mean ± SD of CEA
Control Group	35	11.367 ±0.54 b
Benign Group	35	16.442 ±0.81 b
Malignant Group	35	41.983 ±2.51 a
LSD Value	--	5.771 **
P-Value	--	0.0001
Different letters at the same column Means differed significantly. ** (P≤0.01).		

Estimation of MUC1 Levels by ELISA

ELISA test was performed to estimate Mucin1 levels in serum samples of 35 BC patients, 35 women with benign tumor and 35 healthy women as control group using "Mucin1 ELISA kit", The findings showed that Mucin1 levels were increased in malignant group with mean of about (33.45 ng/ml) and (5.56 ng/ml) benign group and (2.81 ng/ml) for control group (p<0.01) as shown in (Table 5).

Table 5: The mean of MUC1 serum levels in all groups

Group	No.	Mean ± SD of MUC1
Control Group	35	2.81 ±0.08 b
Benign Group	35	5.56 ±0.32 b
Malignant Group	35	33.45 ±1.89 a
LSD Value	--	4.062 **
P-Value	--	0.0001 **
Different letters at the same column Means differed significantly. ** (P≤0.01).		

Estimation of AKT Levels by ELISA

ELISA test was performed to determine Protein Kinase B(AKT) levels in samples of 35 BC patients, 35 women with benign tumor and 35 control using "AKT ELISA kit", The findings showed that AKT level was increased in malignant group with mean of about (3.174ng/ml) and (2.237ng/ml) benign group and (1.510 ng/ml) control group (p<0.01) as shown in (Table 6).

Table 6: The mean of AKT serum levels in all groups

Group	Number	Mean ± SD of AKT
Control Group	35	1.510 ± 0.07 b
Benign Group	35	2.237 ± 0.17 ab
Malignant Group	35	3.174 ± 0.22 a
LSD Value	--	1.173 **
P-Value	--	0.0095
* Different letters at the same column Means differed significantly. ** (P≤0.01).		

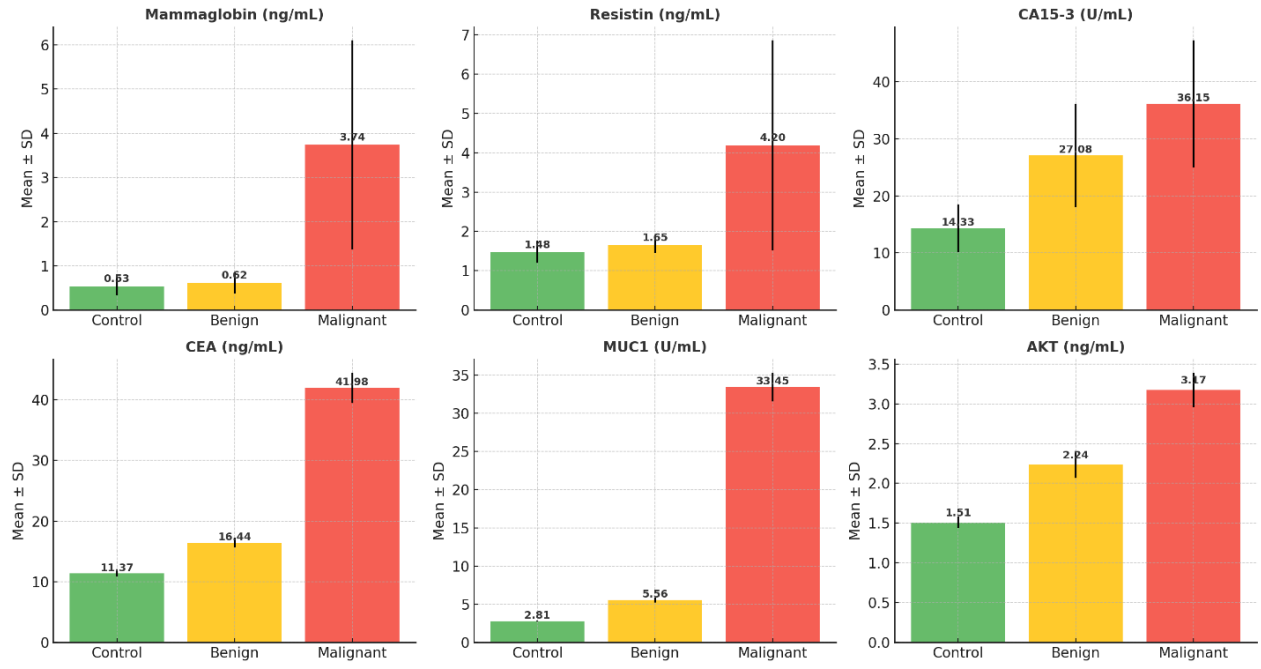

Figure 1: the graph above is a bar chart comparing the concentration of six biomarker in control, benign and malignant groups; Mammaglobin, Resistin, CA15-3, CEA, MUC1 and AKT (Graph Pad Prism 9.3.1(47).

4.2.8 Comparison of ROC curves for six biomarkers

The preceding figures illustrate the receiver-operating characteristic (ROC) curves for the six analyzed parameters. These ROC curves were constructed using Graph ROC software (Windows version), with the corresponding areas under the curve (AUCs) computed to evaluate diagnostic performance and enable pairwise comparisons between individual parameters' AUC values. Fig 1 is representing the graph which is a bar chart comparing the concentration of six biomarker in control, benign and malignant groups; AKT, CA15-3, CEA, Mammaglobin, MUC1 and Resistin. Fig 2 presents the specificity (SP) and sensitivity (SE) values for all analyzed parameters. The results demonstrated that CEA and MUC1 exhibited the highest combined sensitivity and specificity among all evaluated markers in the total cancer cohort. The ROC curve graphically represents the inverse relationship between diagnostic sensitivity and specificity. The area under the ROC curve (AUC) serves as an indicator of a tumor marker's diagnostic performance and clinical value. An AUC of 0.5, represented by the diagonal reference line on the ROC plot, indicates a complete lack of discriminatory power between affected and unaffected individuals. The study refers to these tumor markers in combination may be a useful way for prognosis, detection and also follow up of BC. CEA and MUC1 are the best markers in their sensitivity and specificity. (Table 7) [28,29]. Fig 2: Representing

Receiver Operator Characteristics curve (ROC) for distin- guishing between Studied Groups.

Table 7: Comparison of Area Under the ROC Curve (AUC)(95% CI) Values of Six Serum Biomarkers in Differentiating Benign and Malignant Cases.

Marker	AUC (95% CI) – Benign	AUC (95% CI) – Malignant
Resistin	0.678 (0.550–0.790)	0.967 (0.910–0.990)
Mammaglobin	0.560 (0.430–0.680)	1.000 (0.950–1.000)
CA15-3	0.904 (0.850–0.950)	1.000 (0.960–1.000)
MUC1	0.997 (0.960–1.000)	1.000 (0.970–1.000)
CEA	0.999 (0.970–1.000)	1.000 (0.980–1.000)
AKT 0.986 (0.940–1.000) 1.000 (0.960–1.000)		

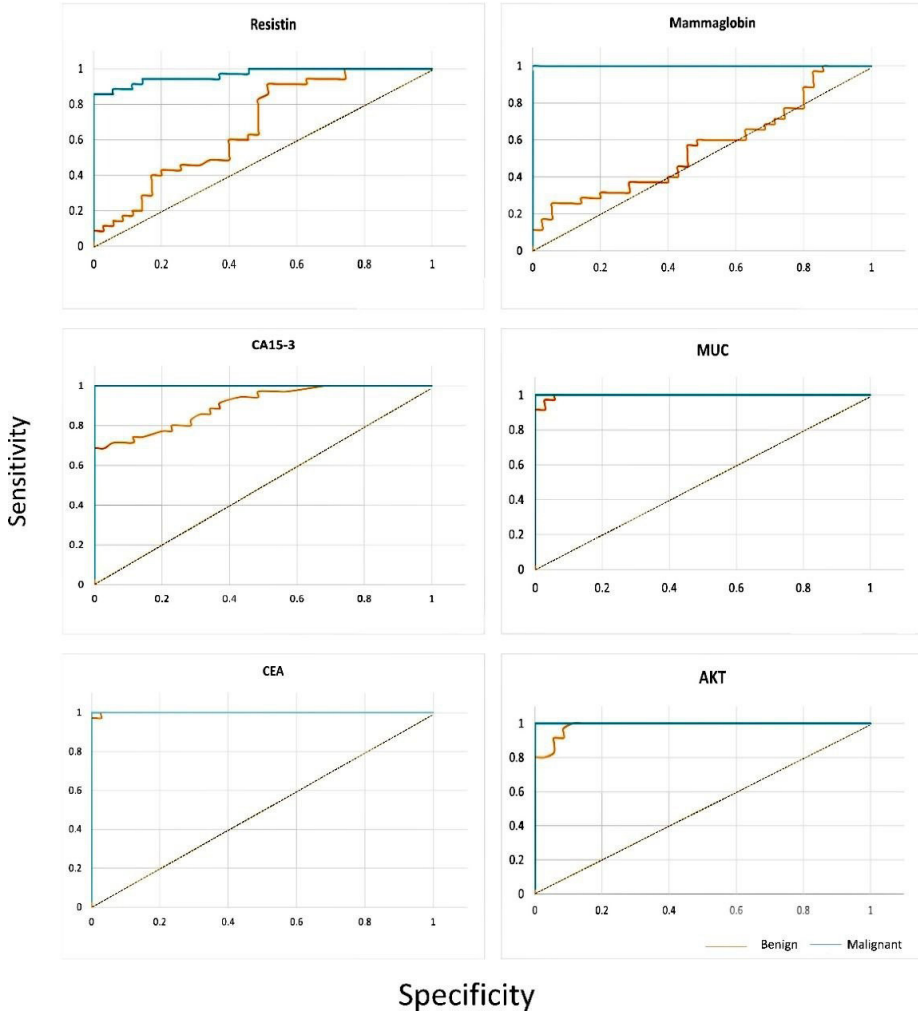

Figure 2: Receiver Operator Characteristics curve (ROC) for distinguishing between Studied Groups. Concentration of six biomarker in benign and malignant groups; CEA, MUC1, AKT, and CA15-3 show almost perfect separation (AUC ≈ 1), demonstrating excellent diagnostic performance. Mammaglobin shows weaker performance in benign vs malignant discrimination (AUC closer to 0.5–0.6). Resistin performs moderately well (AUC ≈ 0.67 for benign, ≈0.97 for malignant). Thus, the figure highlights that CEA, MUC1, AKT, and CA15-3 are the most reliable serum biomarkers for distinguishing malignant cases, whereas Mammaglobin and Resistin provide lower diagnostic accuracy. X-axis: Specificity (False Positive Rate) Y-axis: Sensitivity (True Positive Rate).

Discussion:

Mammaglobin have been identified as a stable and potentially important noninvasive biomarker for BC, based on a comparative analysis using ELISA test to measure serum levels of mammaglobin in both BC patients and healthy control [10; 11]. The concentration of mammaglobin significantly increases during breast cells proliferation, with production ceasing when breast epithelial cells differentiate, a process also seen during lactation. This indicates that mammaglobin synthesis plays a role in the proliferation of epithelial breast cells, which may explain its overexpression in BC [12]. Another study has provided strong evidence proving that some mammaglobin proteins are associated with the membrane. Based on the finding that human mammaglobin possibly exists on the surface of BC cells, Li and Zhang (2016) suggest that the presence of membrane-associated mammaglobin could be a valuable molecular target for future development of therapeutic tools [13]. Elevated serum resistin levels have been associated with enhanced tumor progression and reduced survival in breast cancer (BC), particularly among obese individuals. Clinical studies indicate that postmenopausal BC patients exhibit significantly higher circulating resistin concentrations compared to both premenopausal BC patients and cancer-free postmenopausal controls, suggesting a potential role of resistin in obesity-associated BC pathogenesis.[14]. Emerging evidence suggests that resistin may function as a valuable diagnostic and prognostic biomarker in breast cancer, given its association with tumor progression and poor clinical outcomes. [15]. Resistin has been associated with an increased risk of progression, angiogenesis and metastasis in different cancer models including breast cancer. It also plays a role in chemoresistance and stemness induction in breast cancer. A study involved (80) BC patients and (50) healthy controls revealed higher resistin levels compared to healthy individuals. Clinical studies demonstrate a significant association between elevated serum resistin levels and lymph node metastasis in breast cancer patients. These findings suggest resistin's potential role as an independent risk factor in breast cancer progression. [16, 17 and 30, 31]. In the context of metastasis, which is a leading cause of cancer-related deaths, resistin has been shown to be elevated in postmenopausal BC patients with distant metastasis. In BC cells, resistin promotes the phosphorylation of key proteins (such as c-src, PP2A, and PKCα) and increases the expression of vimentin, all of which facilitate cell invasion and metastasis [18]. A comprehensive meta-analysis established that both CA15-3 and CEA serve as significant prognostic biomarkers for poor Disease-Free Survival and Overall Survival when irregular levels were observed in BC patients. Elevated CA15-3 and CEA were closely associated with age and tumor size [19]. It's not yet clear how CA15-3 have the ability of prognosis in BC, but there is some evidence that it could be related to the structure; The biological function of CA15-3, as a soluble form of MUC1 (a non-gel-forming mucin), may underlie its clinical significance in breast cancer progression. Mechanistic studies suggest that CA15-3 contributes to tumor aggressiveness through multiple pathways: Immune Evasion – By masking tumor-associated antigens, it helps cancer cells avoid immune surveillance and destruction. Metastatic Promotion – CA15-3 interacts with membrane receptors, activating pro-migratory signaling pathways that enhance cancer cell invasion and dissemination. Tumor Microenvironment Modulation – Its presence may facilitate cell-adhesion changes, supporting metastatic niche formation.[20]. CA15-3 has emerged as the most widely utilized circulating tumor marker in breast cancer (BC), with its clinical utility stemming from a strong correlation with disease burden. Key observations include: Tumor Burden Association and Disease Stage Specificity. Furthermore, patients who had elevated CA15-3 levels before tumor resection were more likely to experience increased levels of CA15-3 at the time of recurrence. The changes in CA15-3 levels are closely related to the clinical response to treatment and survival benefit especially in metastatic BC of Luminal subtypes rather than the initial CA15-3 levels. Consequently, measuring CA15-3 levels at regular intervals after the initiation of systemic therapy has shown as effective as medical imaging at a lower cost, potentially allowing it to predict clinical responses and serve as an alternative to imaging technologies such as CT scan, PET, and MRI [21; 22]. Serum tumor markers commonly used in breast cancer (BC) include carcinoembryonic antigen (CEA). Some studies suggest that CEA is not a reliable predictor in primary or metastatic BC [26], while others report that elevated CEA levels are associated with poor prognosis [27]. These inconsistencies may be attributed to factors like small sample sizes, differing study designs, or biases in individual studies. Elevated serum tumor marker levels typically reflect a higher tumor burden, which is linked to larger tumor size, lymph node involvement, and poorer survival outcomes in breast cancer (BC). The study results showed that rising levels of biomarkers like CA15-3 and CEA were strongly correlated with tumor progression and advanced TNM staging. Specifically, higher levels of these markers were observed in cases of larger tumors, positive lymph node metastasis, and advanced TNM stages, suggesting a direct relationship between elevated tumor biomarker levels and overall tumor load. Mucin1 (MUC1), a transmembrane glycoprotein frequently dysregulated in cancers, enhances the invasiveness and metastatic potential of adenocarcinomas by disrupting cell-cell and cell-extracellular matrix adhesion. It serves as a prognostic biomarker in both early and advanced breast cancer (BC). Most studies evaluating MUC1 in non-metastatic BC patients have analyzed blood samples collected prior to surgery. However, one study demonstrated that post-surgical (but pre-chemotherapy) MUC1 levels offer additional prognostic insights beyond conventional clinical factors, whereas post-chemotherapy measurements did not provide further predictive value compared to pre-treatment levels [20]. In addition to its prognostic utility and therapeutic potential in cancer, MUC1 plays a key role in

immune regulation, including infection defense, inflammation modulation, and T-cell regulation as a checkpoint molecule. The association between low MUC1 expression and adverse outcomes in node-positive patients with advanced-stage tumors (pT3/4) may stem from impaired immune regulatory functions. Diminished co-stimulatory and co-inhibitory signaling by MUC1 could disproportionately impact patients with lymph node metastasis and aggressive disease. While large-scale analyses revealed no prognostic relevance of MUC1 in node-negative cases, a significant correlation was observed in node-positive cohorts [23]. However, these findings should be interpreted with caution due to the risk of overfitting associated with our relatively small sample size. The Akt/protein kinase B (PKB) Akt is a key regulator of cell survival. A significant increase in Akt kinase activity has been observed in 30% to 40% of breast cancer (BC) samples. Constitutive activation of Akt and other components in the Akt pathway is seen in both early-stage (in situ) breast carcinoma and invasive breast cancer. Importantly, Akt activation contributes to resistance to anti-estrogen therapies like tamoxifen, a key drug for hormone receptor-positive breast cancer, and plays a role in resistance to chemotherapy and radiation treatments [24]. Given its role in breast cancer progression and treatment resistance, Akt is considered a promising target for new therapeutic strategies. The PI3K/Akt/mTOR signaling pathway is commonly activated in breast cancer, driven by membrane receptors such as IGF and EGF receptor family members. Dys-regulation of this pathway is closely linked to tumor progression and resistance to conventional treatments, making it a central focus in efforts to overcome drug resistance [9, 25].

Conclusion

The present study demonstrates that these tumor markers in combination may be a useful way for detection BC. The six biomarkers AKT, CA15-3, CEA, Mammaglobin, MUC1, and Resistin show promise in differentiating between control, benign, and malignant breast conditions. They may aid in early detection, screening, prognosis, treatment monitoring, and follow-up. CEA and MUC1 are the predictive markers in their sensitivity and specificity. These findings highlight their potential as complementary tools in comprehensive breast cancer care. To establish them as reliable clinical tools, external validation in larger, prospective cohorts is an essential next step.

Study Limitations: This study is limited by its single-center design and moderate sample size, which may restrict the generalizability of our findings. The lack of long-term follow-up prevents assessment of outcome durability or late effects, while the absence of molecular subtype stratification represents a key constraint in understanding the impact of tumor biology.

Author Declarations

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Conflict of interest

The authors affirm no conflicts of interest concerning this publication. This research was solely supported by funding from Dr. Khadija Abbas Sahan. The authors further confirm the absence of any financial or personal affiliations that could be perceived as influencing the findings presented in this work.

Ethics Statement

This study was conducted in accordance with ethical standards and approved by the Ethical Committee of the University of Baghdad (Approval No.: 8021; Date: 3 March 2021). All procedures involving human participants were performed in accordance with institutional and international ethical guidelines.

Consent for Publication

All participants provided informed consent for the use of their data for research and publication purposes.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

All authors contributed equally to the study. All authors have read and approved the final version of the manuscript.

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