Metastasis-Associated in Colon Cancer 1 (MACC1) and its Relationship With Breast Cancer

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Abstract

The need for trustworthy indicators for early identification and assessment is highlighted by the fact that breast cancer is still one of the top causes of cancer-related mortality for women globally. This study investigated the role of Metastasis-Associated in Colon Cancer 1 (MACC1) as a potential diagnostic and prognostic biomarker in breast cancer. 66 patients with breast cancer and 35 healthy controls were included in the study. Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was used to evaluate the expression of the MACC1 gene, with the 2-ΔΔCt method, while serum MACC1 protein levels were assessed by enzyme-linked immunosorbent assay (ELISA). Associations between MACC1 expression and clinicopathological factors, including age, marital status, menopause, breastfeeding, smoking, and surgical history, were also analyzed. The results showed a highly significant elevation in both MACC1 mRNA and protein levels in breast cancer patients, particularly in stages III and IV ($P < 0.0001$). ROC analysis demonstrated perfect diagnostic performance (AUC = 1.000). Higher MACC1 levels were associated with postmenopausal status, sebaceous cyst history, and unhealthy diet, whereas lower levels were linked to breastfeeding and mastectomy. Patients also showed elevated inflammatory indices and reduced hemoglobin. Overall, MACC1 appears to be a promising liquid biopsy biomarker for early promp recognition, prognosis, and monitoring of breast cancer progression.

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Introduction

Breast cancer is a leading type of cancer that affects the female population across the globe. With around 685,000 deaths in 2020 alone, this disease has become the second most deadly cancer that affects women. Taking into consideration all the types of cancer, breast cancer is the most widespread and it is responsible for 25% of all cancer cases and 16% of the fatalities due to cancer [1]. Women who are 50 years and older are more likely to develop this disease, but, more recently, younger women are being diagnosed at an alarming rate. When we take a closer look at breast cancer, we will notice that it is made of a diverse pool of cancer cells, the overexpression of a protein known as HER2, and the activation of the progesterone and oestrogen receptors. Mutations in breast cancer predisposition genes, known as BRCA 1 and BRCA 2, are known for producing truncated non-functional proteins that lead to hereditary breast cancer [2].

Metastasis-Associated in Colon Cancer 1 (MACC1) has gained significant attention in recent years, MACC1 is an oncogene first found in colorectal cancer, it has been connected to tumor development, metastasis, and a poor prognosis in a number of solid tumors, including as hepatocellular carcinoma, lung adenocarcinoma, and stomach cancer[3]. The MACC1 gene is located on chromosome 7 (7p21.1), spanning 82.7 kb with seven exons and six introns [4]. MACC1 acts as a transcription factor activating c-MET and the HGF/Met pathway, promotes epithelial-mesenchyme transition (EMT), and regulates multiple stages of metastasis [5,6,7]. High MACC1 expression correlates with increased relapse and reduced survival, therefore, the purpose of this study was to assess the expression of MACC1 in breast cancer tissues and its correlation with clinicopathological characteristics and patient prognosis[8].

Materials and methods

Samples preparation

Sixty-six samples had been collected from breast cancer patients with ages (35–75 years) who visited the Specialized Oncology and Nuclear Medicine Hospital,

And 35 blood samples were collected from healthy women with match age. Serum was separated, by centrifuge and stored at −20 °C, and subsequently used to determine some biochemical variables. Peripheral venous blood samples were obtained from patients using EDTA-anticoagulated tubes and were promptly transferred to the laboratory to perform subsequent genetic analysis.

Methods

Gene Expression Analysis of MACC1

Total RNA was extracted from whole blood samples using TransZol Up Plus RNA Kit as directed by the manufacturer (Transgene Biotech, China). A Nanodrop spectrophotometer was used to measure the absorbance at 260 and 280 nm in order to determine the purity and concentration of RNA. Samples were deemed clean if their A260/A280 ratio fell between 1.8 and 2.0. The EasyScript® One-Step gDNA Removal and cDNA Synthesis Kit was used to eliminate genomic material contamination and create complementary DNA (cDNA).

Quantitative real-time PCR (qRT-PCR) was performed using TransStar® Top Green qPCR SuperMix with specific primers for MACC1 and GAPDH as a housekeeping gene. The 2^−ΔΔCT technique was used to determine the relative levels of gene expression.

ELISA measurement of MACC1 protein

The concentration of MACC1 protein was determined using a commercial ELISA Kit supplied by Bioanlytical Technology Laboratory (China) according to the manufacturer´s instructions. Hematological parameters were obtained from the complete blood count (CBC) using a Sysmex automated hematology analyzer, including WBC, HB, PLT, LYMPH, and NEUT. Inflammatory indices were calculated as follows: NLR = NEUT /LYMPH, PLR =PLT/ Lymph, SII = (PLT ×NEUT)/LYMPH, NPLHbR= (NEUT X PLT)/(Lymph X Hb). In addition, we evaluated the protein expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor2 (HER2) using immunohistochemistry (IHC). Lactate dehydrogenase (LDH) activity was measured using FUJIFILM DRI-CHEM SLIDE LDH-P III slides based on dry chemistry technology (Fujifilm Corporation, Japan) [9]

Table 1. clinical characteristics of patients and control

Clinical variables	Control group mean± S. E	Patients mean± S. E
WBC	7.780 ± 0.2972	5.758 ± 0.3421 **
PLT	302.4 ± 16.74	252.3 ± 10.10*
SII	421.3 ± 34.61	621.2 ± 60.14**
PLR	115.7 ± 10.56	185.7 ± 14.30*

NPLHBR	40.85 ± 5.507	59.64 ± 4.506*
NLR	1.781 ± 0.1839	2.266 ± 0.1180*
Neut	4.422 ± 0.2469	3.342 ± 0.2268
Lymph	2.680 ± 0.1731	1.699 ± 0.09392****
LDH	167.4 ± 12.57	236.8 ± 27.29*
Hb	13.13 ± 0.2468	11.26 ± 0.2918**

*Significant variance p≤0.005, and **p≤0.01, and***p≤0.001, and****p≤0.0001

Date analysis

Statistical analysis was performed using SPSS software. Date was expressed as mean ± standard error (SE). The independent sample t-test was used to compare differences between two groups, whereas one-way ANOVA was used to compare different groups. A statistically significant p-value was defined as ≤0.05. Diagnostic performance was assessed using recover operating characteristic (ROC) curve analysis and the area under the curve (AUC), and the best cutoff value was found using Youden's index.

Results And Discussion

Our data showed a progressive increase in MACC1 gene expression across breast cancer stages compared to the control group as shown in Fig. 1, with the highest levels observed in advanced stages (III and IV). This pattern indicates a strong association between MACC1 expression and tumor progression and may reflect the enhanced metastatic potential of cancer cells in later stages. The use of real-time PCR (qPCR) in blood samples is supported by studies demonstrating that circulating tumor-derived nucleic acids, including MACC1 transcripts, can be reliably detected in blood samples and are significantly elevated in Cancer sufferers in contrast to healthy people. Therefore, measuring MACC1 expression in blood represents a valid, non-invasive approach for monitoring disease progression. [10,11]

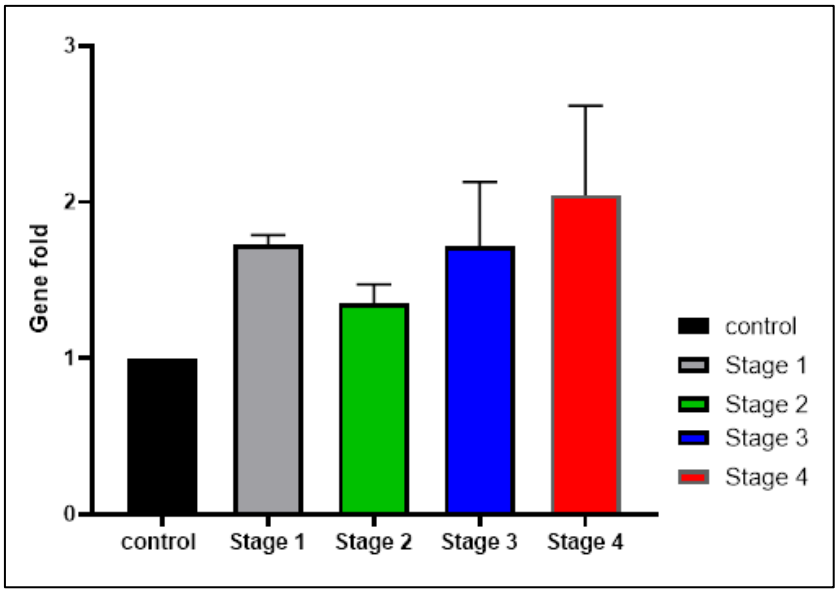


Fig. 1: Relative MACC1 gene expression levels across different stages of breast cancer

Macc1 concentration in Breast cancer with the control group

Serum MACC1 levels, determined using the ELISA technique, showed a significant increase at (P≥ 0.0001) in breast cancer patients (1828 ± 154.7 pg/mL) compared to the control group (244.7 ± 8.527pg/mL), as presented in Fig. 2. This observation is in agreement with previous studies [12,13], which also demonstrated elevated MACC1 levels in individuals with breast cancer, supporting its potential as a biomarker for prognosis and diagnosis. Furthermore, the increased MACC1 expression may reflect its role in promoting tumor proliferation, metastasis, and angiogenesis, highlighting its clinical relevance in breast cancer progression and patient management.

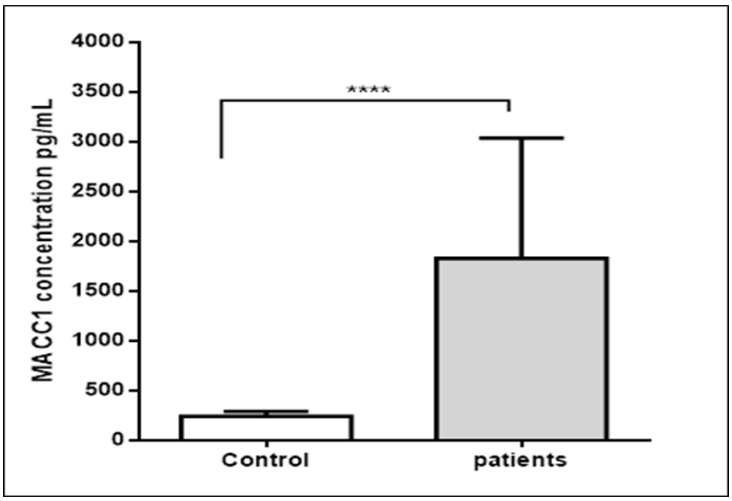


Fig. 2. MACC1 concentration in breast cancer compared to healthy

Association between Serum MACC1 Levels and Clinicopathological Parameters in Breast Cancer Patients

As seen from the data in Table 4, there is a commensurate rise in serum MACC1 protein concentration in parallel with progression in breast cancer, with the protein levels being the lowest in stage I and II malignancies, whereas there is a considerable rise in stage III and IV cancers. This trend indicates that there is a close association between the expression of MACC1 and the extent of tumor progression that may be a consequence of the larger tumor sizes coupled with a more aggressive biological behavior in the latter stages of the disease.

From a biological perspective, MACC1 is categorized as an oncogene and plays a pivotal role in the operation of tumorigenesis as it activates the HGF/MET pathway which in turn leads to enhanced proliferation, migration, and invasion of cancer cells. Elevated MACC1 expression has also been shown to facilitate epithelial-mesenchymal transformation (EMT), thus contributing to metastasis and tumor progression.

Similar previous studies have reported that elevated serum MACC1 levels are strongly associated with advanced TNM stage (as shown in Figure 2), tumor size, lymph node metastasis, and poor prognosis in breast cancer patients. These results support the potential role of MACC1 as a promising biomarker for tumor progression and disease severity in breast cancer [14, 15, 13]. According to these results, patients had been divided into two groups, stage I and II patients (stage I+II) and stage III and IV patients (stage III+VI)

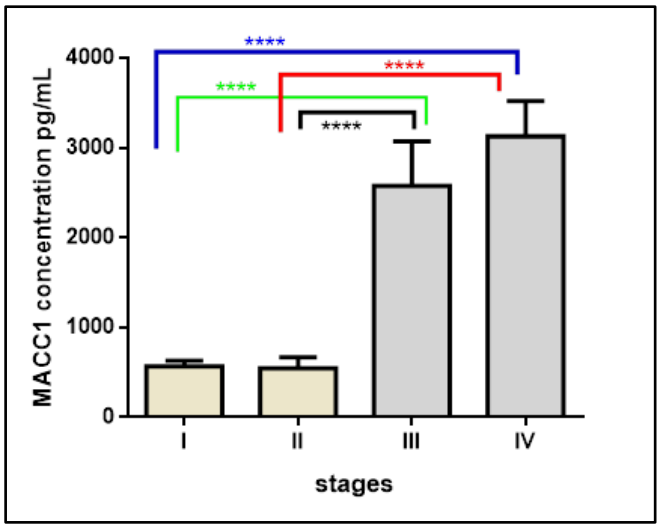


Table 4. Macc1 concentration in patients according to disease stage

As shown in Table 2, the results showed a non-significant difference in serum MACC1 levels in patients according to age, which is in agreement with [16] and may indicate that the expression of this biomarker is more closely related to tumor progression and metastatic potential rather than demographic characteristics such as age. Several studies have reported that MACC1 expression is significantly associated with tumor stage, lymph node metastasis, and aggressive tumor behavior, rather than patients' age. Furthermore, MACC1 has been shown to promote tumor growth, invasion, and metastasis through activation of the HGF/c-MET signaling pathway, which plays a crucial role in cancer progression [17,14]. It seems like postmenopausal women have higher levels of MACC1. This may be due to hormonal changes that affect how a tumor develops. Menopausal status impacts how much MACC1 is

expressed. A reduction in sex hormones is likely responsible for the increase in levels of MACC1 in postmenopausal women. Without protective mechanisms from estrogen, breast cancer cells may activate the MACC1/HGF/MET pathway to promote their own survival, as well as for Epithelial-Mesenchymal Transition (EMT), and for the outspread of the cancer to other tissues [18].

Also, the increase in postmenopausal status and MACC1 level explains why malignant tumours in this population are common. For a tumour to be invasive and for angiogenesis to occur, MACC1 needs to be abundant. The presence of MACC1 at high levels in the serum is indicative of a positive liquid biopsy and serves as a non-invasive way to measure potential metastasis in postmenopausal women, which in turn helps to optimize clinical management and tailoring of therapeutic approaches [19].

Table 3. MACC1 Concentration according to clinical variables

Variables	MACC1 (Pg/ml)			
	Patients stage I +II	p-value	Patients stage III +IV	p-value
Age (years) 35- 45 46-56 >57	 557.3 ± 29.26 485.2 ± 37.99 591.4 ± 30.39	 0.1567	 2879 ± 89.28 3162 ± 131.6 2726± 133.2	 0.1341
Menopausal status Pre Post	 518.9 ± 19.89 611.3 ± 31.91	 **0.0157**	 2486 ± 172.2 3030 ± 77.97	 **0.0023**
mode of delivery VD C-section	 558.3 ± 27.48 561.3 ± 39.10	 0.9537	 2166 ± 200.4 3078 ± 89.76	 **< 0.0001**
lactation history breastfeeding formula-feeding	 504.5 ± 28.35 610.5 ± 33.71	 **0.0278**	 2381 ± 197.7 3050 ± 87.89	 **0.0012**
Dietary habits Healthy Unhealthy	 546.5 ± 21.31 559.4 ± 24.31	 0.7875	 2512 ± 172.5 2994 ± 89.09	 **0.0096**
Smoking status Smoker Non-smoker	 603.8 ± 54.79 543.0 ± 19.23	 0.1974	 2657 ± 161.9 2877 ± 102.8	 0.3589

VD: Vaginal Delivery; C-section: Cesarean Section;

Breast cancer patients exhibited progressively elevated MACC1 levels, particularly in advanced stages of the disease. There appears to be a significant difference in the level of MACC1 between Vaginal Delivery compared to C-Section in patients in stage III+IV, with higher MACC1 levels reported in women with a previous C-Section compared to those with a C-Section. Some authors have proposed that due to cesarean delivery having the potential to initiate a systemic inflammatory response and modify the post-operative hormonal changes, cesarean delivery as a reproductive factor may be linked to having more aggressive pathological features. Hence, concerning patients with advanced stages of cancer, the presence of higher MACC1 as a result of having cesarean delivery, may indicate the interplay of reproductive history with the malignant evolution of cancer [20].

This research aimed to evaluate the levels of serum MACC1 as they related to different feeding types. Results indicate that study participants with an extended duration of breastfeeding practice, had significantly lower levels of MACC1 compared to participants in the formula feeding group. It is said that breastfeeding protects mothers against breast carcinogenesis. This is because it limits the total time of exposure to estrogen and helps in the normal differentiation of mammary cells which in turn decreases the chances of malignant transformation. Moreover, there is a physiological change in the breast during lactation that assists in removing the potentially damaged cells or those with mutations in the genetic code. In addition, recent research shows that lactation may stimulate the immune cells within the breast, thereby increasing the breast tissue immune response and the tumor growth-suppressive cells. Nutrition in this study was evaluated using the Food Frequency Questionnaire (FFQ). The study participants were divided into two cohorts, those with a Healthy Dietary Pattern (high in antioxidants and fibers) and the Unhealthy Dietary Pattern (high in processed meat and refined sugary products).

The data in Table 3 shows that participants with a Healthy Dietary Pattern had higher levels of MACC1 in serum compared to those with a Healthy Dietary Pattern during stage III+IV, and therefore, there is a likelihood of association between the dietary patterns and the progression of the disease in the patients. Unhealthy Dietary Patterns in food consumption, which are characterized by the superfluous use of processed and saturated fat foods are major contributory factors to ignite chronic inflammation and oxidative stress which are the cornerstones for tumor growth and the spread of metastasis.

On the other hand, the anti-inflammatory properties and the ability to improve cellular control and reduce the quantity of MACC1 protein, and hence reduce the risk of breast cancer, may be attributed to the healthy anti-inflammatory and cellular control-rich diets. [22,23]

The findings showed no statistically significant difference regarding serum MACC1 levels between the smoker and the non-smoker participants. The effect of surgical procedure was analyzed on MACC1 serum levels in BC patients (stage III+IV). A statistically significant difference was noted between study groups, where the mastectomy patients had lower mean serum levels of MACC1 compared to non-mastectomy patients, as illustrated in Figure 3. This finding suggests that the presence of the primary tumor contributes to elevated circulating MACC1 levels, reflecting tumor size and metastasis potential. Therefore, surgical intervention for the tumor may contribute to lowering circulating MACC1 levels and potentially limiting disease progression, which is consistent with clinical evidence indicating that primary tumor resection in breast cancer improves outcomes and reduces the risk of metastasis.[24]

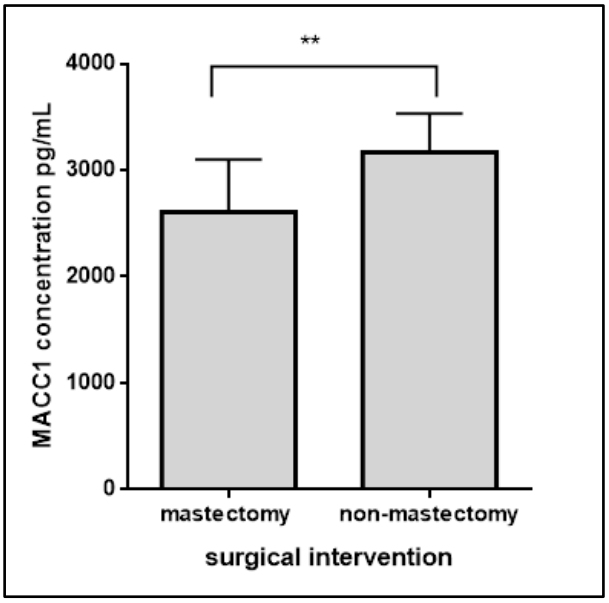


Fig. 4: The impact of surgical intervention on serum MACC1 levels in the BC patients at stage III+IV

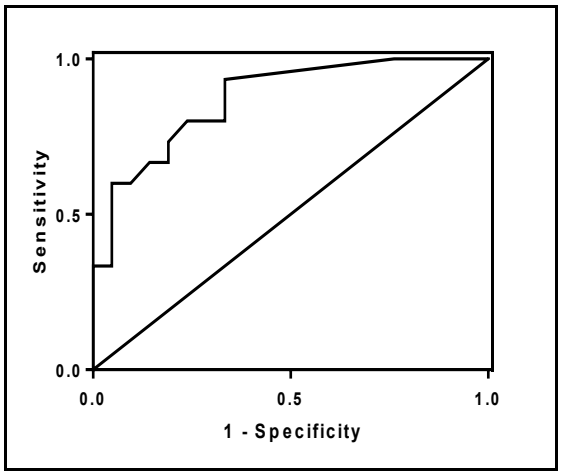
Receiver Operating Characteristics (ROC) Curve for MACC1 Level in BC patients:

The ROC curve shown in Figure 5 (a, b, c, d) was used to determine the optimal cutoff value for distinguishing between breast cancer patients in stages one, two, three and four and the healthy control group, as show in the table below:

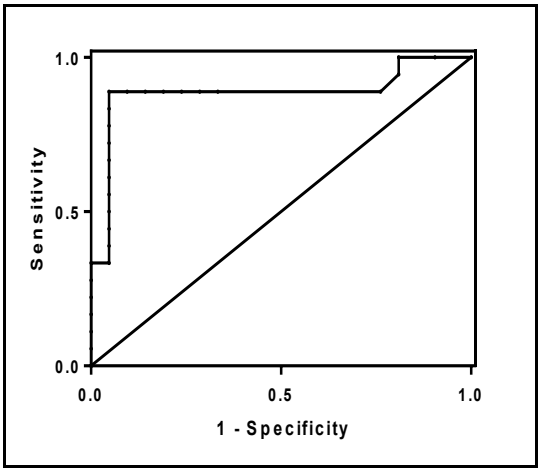
Table(4) shows the values of the ROC curves for the MACC1 protein in breast cancer patients across the four stages

Stage	Value of the pieces pg/ ml	AUC	95% confidence interval	sensitivity	specificity	P_ value
Stage I	305.0	0.871	0.757 0.985	0.8	0.76	0.0001
Stage II	353.8	0.884	0.758 1.0	0.88	0.95	0.001
Stage III	851	0.88	0.784 0.982	0.769	1	0.001
Stage IV	1075	0.972	0.93 1.0	0.863	1	0.001

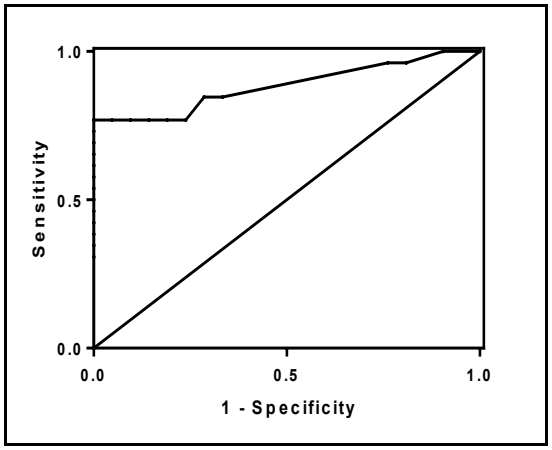
As show in the figures below :



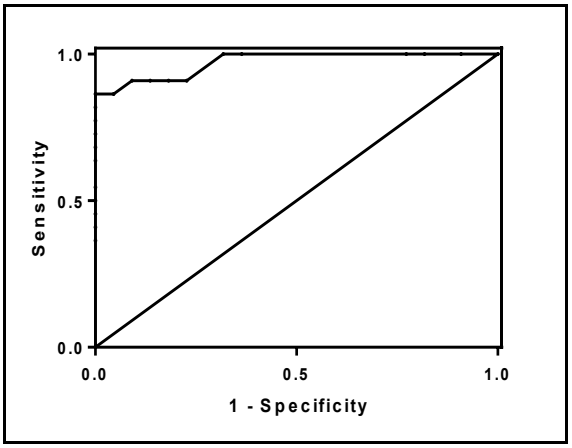
(A) BC patients at stage I



(B) patients at stage II



(C) BC patients at stage III



(E) BC patients at stage IV

Figure (5) ROC curve of BC patients

Table 4 demonstrates the diagnostic and prognostic performance of MACC1 protein across different stages of breast cancer. The results showed a progressive increase in the area under the curve (AUC) from 0.871 in stage I to 0.972 in stage IV, indicating enhanced discriminatory ability with disease advancement. Similarly, the optimal cut-off values increased from 305.0 pg/ml to 1075 pg/ml across stage, accompanied by improved specificity, reaching 100% in stages III and IV while maintaining high sensitivity. These findings suggest that elevated MACC1 expression is strongly associated with tumor progression and advanced disease status. The high specificity observed in later stages highlights the potential utility of MACC1 as a reliable biomarker for identifying patients with aggressive or metastatic breast cancer, supporting its value in disease monitoring and prognostic assessment.

Conclusions

The study concludes that MACC1 (both gene and protein levels) serves as a high-precision biomarker for breast cancer detection. The ROC curve analysis yielded an ideal AUC of 1.000, demonstrating its perfect ability to discriminate between cancer patients and healthy individuals. MACC1 levels showed a significant progressive increase across clinical stages, peaking at stages III and IV. This underscores its pivotal role in driving tumor aggression and metastatic potential. Postmenopausal, history of C-sections, and unhealthy dietary habits were linked to higher MACC1 expression, particularly in advanced stages. Serum MACC1 levels reduced significantly in Breastfeeding status and BC patients following mastectomy. Therefore, MACC1 can be considered a promising biomarker in the diagnosis of breast cancer and the assessment of disease progression

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Conflict of Interests

The authors declare no conflicts of interest.

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Ethical Consideration

The College of Education for Women/University of Mosul's Research Ethics Committee authorized the study protocol (Approval No. 44279, dated: October 7, 2025). Prior to sample collection, informed permission was acquired from each participant.

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