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RESEARCH ARTICLE

Serum Oncostatin M Levels are Associated with Insulin Resistance and Clinical Severity in Iraqi Women with Breast Cancer: A Case-Control Study

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Abstract

Introduction: Breast cancer (BC) is a diverse disease characterized by the uncontrolled growth of mammary cells, resulting in tumors with invasive and metastatic capabilities. The advancement of this disease is affected by intricate signaling networks, as Oncostatin (OSM) is a pleiotropic cytokine that regulates inflammation, proliferation, and differentiation. This study aimed to evaluate serum Oncostatin M (OSM) levels in Iraqi women with breast cancer and investigate its correlation with insulin resistance (IR) and disease progression across different clinical stages. Furthermore, the study explores the potential of the OSM pathway as a future therapeutic target. **Materials and Methods:** In a case-control design, 90 newly diagnosed triple-negative BC patients (Stages I–IV) were compared with 90 age-matched healthy controls. Serum OSM and insulin were measured using ELISA, while fasting serum glucose (FSG) and liver enzymes (ALT, AST, ALP) were determined spectrophotometrically. Metabolic indices, including HOMA-IR, HOMA-β, and HOMA-S%, were calculated. **Results:** Serum Oncostatin M (OSM) levels were significantly elevated in BC patients (120.46 ±pm 18.97 pg/mL) compared to healthy controls (70.16 ±12.50 pg/mL; $P < 0.001$). A stepwise progressive increase in OSM was observed alongside advancing tumor stages (I–IV). BC patients exhibited marked metabolic and hepatic disruption, evidenced by significantly higher FSG, insulin, HOMA-IR, and liver enzymes, with a concomitant decrease in HOMA-S% ($P < 0.001$). Strong positive correlations were found between OSM and both HOMA-IR ($r = 0.733$) and insulin ($r = 0.721$). ROC analysis demonstrated excellent performance for OSM (AUC = 0.927), with 89.7% sensitivity and 84.3% specificity at an exploratory cut-off of 99.46 pg/mL. **Conclusion:** Serum Oncostatin M (OSM) serves as a significant marker of progression in Iraqi women with breast cancer, correlating strongly with insulin resistance. Our findings highlight OSM as a key indicator of the metabolic-inflammatory axis; Further longitudinal studies are warranted to validate its potential as a therapeutic target.

Keywords: Breast cancer- Oncostatin- insulin resistance- Biomarkers- Metabolic Dysregulation- Iraqi population

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Introduction

Breast cancer (BC) remains a significant global health burden, accounting for one in four cancer diagnoses in women and standing as the leading cause of cancer-related mortality worldwide [1]. In 2022 alone, approximately 2.3 million new cases and 660,000 fatalities were reported (Kim et al., 2025b). This growing prevalence is particularly concerning in low- and middle-income nations, including Iraq, where BC represented 35.9% of all female malignancies in 2023 [2, 3]. Emerging data from the region highlight an increasing incidence of advanced-stage diagnoses among younger women, driven by urbanization, lifestyle modifications, and limited access to early detection initiatives [4, 5].

The onset and progression of BC are influenced by a complex interplay of non-modifiable factors such as age and genetic predisposition and modifiable metabolic risks [6]. Recent studies emphasize the pivotal role of metabolic dysregulation and obesity in facilitating a tumor-promoting

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environment [7]. Excess visceral adiposity contributes to chronic low-grade inflammation and hyperinsulinemia [8]. Through interaction with the insulin receptor (INSR) and the IGF system, insulin promotes cell proliferation and inhibits apoptosis by activating the PI3K/Akt and MAPK signaling pathways [9]. Consequently, insulin resistance (IR) not only aids disease initiation but also contributes to therapeutic resistance, positioning the insulin pathway as a critical target for investigation [10].

A key molecular mediator in this metabolic-inflammatory axis is Oncostatin M (OSM), a 28-kDa pleiotropic cytokine belonging to the interleukin-6 (IL-6) family. Predominantly produced by activated immune cells, OSM signals through heterodimeric receptor complexes (OSMR/gp130 or LIFR/gp130), activating downstream cascades such as STAT3 and SOCS3 [11, 12]. While OSM serves diverse physiological roles, including hematopoietic and cardiovascular regulation [13]. it is increasingly recognized for promoting tumor aggressiveness. OSM has been shown to induce epithelial-mesenchymal transition (EMT), angiogenesis, and invasiveness in BC cells [14]. Its circulating levels appear to rise alongside advancing tumor stages, suggesting its potential as a prognostic indicator.

Despite its clinical relevance, the relationship between circulating OSM and systemic metabolic disruption in Iraqi BC patients remains under-explored. Therefore, this study aimed to evaluate serum OSM levels in Iraqi women with BC to investigate its correlation with insulin resistance (IR) and disease progression across clinical stages. Furthermore, the study explores the potential of the OSM pathway as a future therapeutic target and a prognostic biomarker for monitoring disease advancement.

Materials and Methods

Study Design and Participants

This case-control study, conducted in Najaf, Iraq (April–October 2025), included 180 women aged 45–60 years. The patient group comprised 90 women with newly diagnosed Triple-Negative Breast Cancer (TNBC), stratified into Stage I (n=25), II (n=25), III (n=20), and IV (n=20), while 90 age-matched, apparently healthy females served as controls. All BC diagnoses were pre-established via mammography and confirmed by histopathological biopsy (ER-/PR-/HER2-negative) prior to blood collection, ensuring that serum OSM measurements reflect the metabolic-inflammatory profile of this specific aggressive subtype.

Exclusion Criteria

Participants were excluded if they had cardiovascular disease, Type 2 diabetes, active infections, or autoimmune disorders. Additionally, individuals with hypertension, or renal, hepatic, or thyroid dysfunction were excluded. Those receiving hormonal therapies (e.g., contraceptives, HRT), lipid-lowering medications, or any treatment affecting metabolic markers were also omitted to minimize confounding variables.

Data and Sample Collection

Demographic and clinical data, including age, family history, and medical records (tumor size, grade, and stage), were collected from all participants using a standardized questionnaire and hospital databases. Anthropometric measurements, including Body Mass Index (BMI), were calculated as weight (kg) divided by height squared (m^2).

Following diagnosis but prior to any therapeutic intervention, 5 mL of fasting venous blood was collected from each participant using gel-clot activator tubes. Samples were allowed to clot at room temperature for 15 minutes, then centrifuged at 3000 rpm for 10 minutes. The separated serum was subsequently aliquoted into Eppendorf tubes and stored at -80°C until analysis.

Immunological and Routine Assays

Serum Oncostatin M (OSM) and fasting insulin (FIN) levels were determined using enzyme-linked immunosorbent assay (ELISA) kits (Pars Biochem, China) according to the manufacturer's protocol. Fasting serum glucose (FSG) and liver function tests (AST, ALT, and ALP) were measured spectrophotometrically using the Roche/Hitachi Cobas c system. Metabolic indices were calculated as follows:

Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) measured = (Fasting serum glucose [mg/dL] x Fasting serum insulin [µIU/mL]) / 405, Insulin resistance was defined as a HOMA-IR value ≥2.7.

Homeostasis Model Assessment of Beta-cell function (HOMA-β) was calculated by the equal HOMA-β = ({360 x insulin [µIU/mL] / (glucose [mg/dL] – 63)} and Homeostatic Model Assessment for Insulin Sensitivity (HOMA-S%) = ([1 / {HOMA-IR}] x 100) Matthews et al., 1985).

Statistical Analysis

Data were analyzed using SPSS version 27. Continuous variables are expressed as Mean ± SD. Data normality was assessed via the Kolmogorov-Smirnov test. Differences between the two groups were evaluated using independent t-tests, while one-way ANOVA followed by Tukey's post-hoc test was used for multi-group comparisons across cancer stages. Categorical data were assessed using the Chi-square test. Correlations between OSM and clinical parameters were determined using Spearman's rank correlation coefficient to ensure robustness against outliers. The diagnostic performance of OSM was evaluated using Receiver Operating Characteristic (ROC) curve analysis, determining the Area Under the Curve (AUC), sensitivity, and specificity. Statistical significance was set at $P < 0.05$.

Results

Patient Characteristics and Biochemical Profile

The study included 90 breast cancer (BC) patients and 90 age-matched healthy controls. As shown in Table 1, serum Oncostatin M (OSM) levels were significantly elevated in BC patients (120.46 ±18.97 pg/mL) compared to the control group (70.16 ±12.50 pg/mL; $P < 0.001$).

Table 1. Comparison of Biochemical Parameters between Patients and Control Groups

Variables	Patients group (Mean ± SD)	Control group (Mean ± SD)	P-value
Number	90	90	--------
Age (years)	54.6 ± 5.9	53.8 ± 6.2	0.32
BMI (kg/m²)	30.7± 3.4	29.13± 2.77	0.051
ALT (IU/L)	30.4± 7.69	17.46± 4.36	< 0.001
AST (IU/L)	36.68± 9.52	22.25± 4.75	< 0.001
ALP (IU/L)	122.86± 29.10	88.42± 22.83	< 0.001
FBG (mg/dL)	112.5 ± 16.9	94.2 ± 11.6	< 0.001
Insulin (µIU/mL)	12.35± 2.99	7.29± 1.57	< 0.001
HOMA-IR	2.78± 0.83	1.25± 0.34	< 0.001
HOMA-β	80.72± 23.96	82.21± 16.34	0.471
HOMA-S(%)	75.85 ± 6.86	102.26± 25.72	< 0.001
Oncostatin M (pg/mL)	120.46 ± 18.97	70.16 ± 12.50	< 0.001

Data are represented as Mean ± SD. SD: Standard Deviation; NS: non-significant at P > 0.05. BMI: Body Mass Index; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ALP: Alkaline Phosphatase; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; HOMA-β: Homeostasis Model Assessment of Beta-cell function; HOMA-S%: Homeostatic Model Assessment for Insulin Sensitivity.

This was accompanied by marked metabolic and hepatic dysfunction in the BC group (P < 0.001), characterized by elevated fasting blood glucose (FBG), insulin, HOMA-IR, and liver enzymes (ALT, AST, and ALP). Conversely, insulin sensitivity (HOMA-S%) was significantly lower in patients (P < 0.001), while no significant difference was observed in beta-cell function (HOMA-β; P=0.471).

Progression Across Tumor Stages: Stratification by disease stage revealed a significant, stepwise progressive increase in serum OSM and liver enzyme levels as the tumor stage advanced (Table 2, Figure 1). Serum OSM reached its peak in Stage IV (131.3 ±18.6 pg/mL) compared to Stage I (112.3 ± 15.1 pg/mL). Statistical significance across clinical stages was denoted by distinct superscript letters (a, b, c, d), confirming that metabolic and inflammatory disruption mirrors disease severity. Notably, these changes were observed independently of BMI, which showed no significant variation across stages (P > 0.05).

Correlation Analysis: Pearson correlation analysis (Table 3) demonstrated strong positive associations between serum OSM and markers of metabolic/hepatic disruption, particularly HOMA-IR (r=0.733, P < 0.0001) and insulin (r=0.721, P < 0.0001). A significant inverse correlation was found between OSM and insulin sensitivity (r = -0.592, P = 0.001). The robust relationship between OSM and HOMA-IR is further illustrated in the scatterplot (Figure 2), showing a consistent linear trend without significant outlier effects.

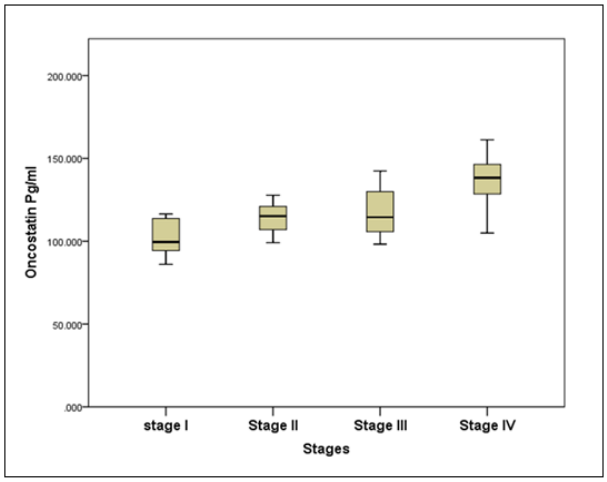

Figure 1. Distribution of Serum OSM Levels Across Different Cancer Stages (I-IV).

Diagnostic Performance

The diagnostic potential of serum OSM was evaluated using Receiver Operating Characteristic (ROC) curve analysis (Table 4, Figure 3). The analysis yielded an excellent Area Under the Curve (AUC) of 0.927 (95% CI: 0.887–0.958, P < 0.001). An exploratory cut-off value of 99.46 pg/mL provided a sensitivity of 89.7% and a specificity of 84.3%. It is important to note that this cut-off is considered preliminary and requires validation in independent cohorts.

Discussion

To our knowledge, this is the first study in Iraq to demonstrate a significant elevation of serum OSM in breast cancer patients compared to healthy controls. These findings suggest a potential link between OSM and disease progression. Furthermore, our results align with emerging evidence indicating that inflammatory cytokines contribute to metabolic dysregulation in malignancy. As reported in previous literature, OSM may influence the tumor microenvironment, although its precise role in survival outcomes requires longitudinal validation [15].

Moreover, the significant correlation between OSM and metabolic dysfunction specifically insulin resistance (IR) and altered liver enzyme activity suggests that OSM may act as a mechanistic bridge connecting systemic inflammation to the tumor's metabolic demands [16]. As an inflammatory cytokine of the IL-6 family, OSM is

Table 2. Comparison of Biochemical Variables between the Different Groups Stages of Breast Cancer Women Group

Variables	Patients Stages			
	Stage I	Stage II	Stage III	Stage IV
Number (%)	25 (27.8 %)	25 (27.8 %)	20 (22.2%)	20 (22.2%)
Age (years)	51.75 ± 5.54 [a]	53.41 ± 4.66 [a]	55.20 ± 5.50 [b]	56.54± 5.85 [b]
BMI (kg/m²)	29.12 ± 3.54 [a]	28.75 ± 3.25 [a]	28.39 ± 3.58 [a]	27.98 ± 3.89 [a]
ALT(IU/L)	18.3 ± 2.11 [a]	25.13± 2.80 [b]	32.89 ± 3.68 [c]	39.27± 3.55 [d]
AST (IU/L)	26.96 ± 3.33 [a]	32.19 ± 5.74 [a]	38.21 ± 7.39 [b]	43.14 ± 7.20 [c]
ALP(IU/L)	105.66 ± 8.21 [a]	115.58± 12.50 [b]	124.7 ±10.62 [c]	135.90±14.46 [d]
FSG (mg/dL)	99.13 ± 7.01 [a]	102.11 ± 8.10 [a]	106.77± 9.25 [b]	112.81 ± 9.71 [b]
Insulin(µU/ mL)	11.64 ± 2.81 [a]	12.36 ± 3.51 [a]	12.96 ± 4.34 [b]	13.76 ± 4.99 [b]
HOMA2-IR	2.04 ± .78 [a]	2.37 ± 0.77 [a]	2.64 ± 0.87 [b]	2.90 ± 0.93 [b]
HOMA2%β	82.29± 25.46 [a]	80.58± 23.88 [a]	76.07 ± 21.41 [b]	70.79 ± 23.54 [b]
HOMA2%S	80.80 ± 5.30 [a]	76.09 ± 5.64 [a]	69.78 ± 5.86 [b]	62.36 ± 5.35 [b]
Oncostatin M (pg/mL)	112.3 ± 15.11 [a]	118.±16 .80 [b]	124.89 ± 17.68 [c]	131.27± 18.55 [d]

Note: Data are presented as Mean ± SD. Means with different superscript letters (a, b, c, d) in the same row indicate statistically significant differences ($P < 0.05$) as determined by Tukey's post-hoc test; conversely, means sharing the same superscript letter are not significantly different.

increasingly recognized for its dual role in carcinogenesis; it is linked to BC growth, invasion, and metastasis, In the context of obesity, adipose-derived inflammation may further boost OSM levels, thereby promoting tumor cell development [17]. Previous data also indicate that while stromal-derived OSM can be context-dependent, it often promotes tumor growth in various malignancies by increasing cancer stem cell populations [14].

The relationship between metabolic health and BC is further highlighted by the association between obesity, type 2 diabetes, and hyperinsulinemia. Insulin resistance (IR) necessitates compensatory hypersecretion of insulin, which can operate as a mitogenic factor, significantly correlating with elevated cancer mortality [18, 19]. This pro-tumorigenic milieu, driven by hyperinsulinemia, increases endogenous estrogen and activates mitogenic pathways, explaining why interventions that improve insulin sensitivity may reduce BC risk [20]

Our results also align with recent studies showing that individuals with IR exhibit elevated serum OSM levels compared to healthy controls [21]. OSM has been shown to disrupt insulin signaling in adipocytes and muscle, worsening systemic IR and reducing glucose uptake [22]. Furthermore, OSM signaling activates MAPK-dependent pathways, maintaining stemness and mesenchymal programs in aggressive BC subtypes [23].

Regarding metastatic progression, recent evidence suggests that IL-6 family cytokines are involved in the formation of bone metastases [24]. In our cohort, we observed a statistically significant increase in alkaline phosphatase (ALP) levels, which is a known sensitive marker for osteoblastic activity during bone invasion [25]. Additionally, the stepwise increase in liver enzymes (ALT, AST, and ALP) paralleled the elevation of serum OSM across BC stages (Table 2). This synchronized trend suggests that OSM-mediated signaling may contribute to hepatic micro-inflammation or the formation of a pre-metastatic niche, serving as a biochemical indicator of subclinical liver involvement [26]. Finally, the interplay between insulin and inflammatory cytokines like IL-6 and OSM appears to foster a pro-angiogenic environment through the PI3/Akt pathway, further facilitating vascular endothelial cell migration and tumor advancement [27].

Limitations and Future Directions

Despite its clinical insights, this study has certain limitations. The case-control design precludes establishing

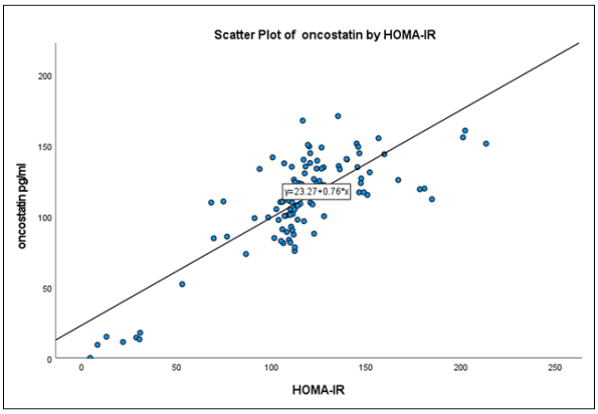

Figure 2. Scatterplot Showing the Positive Correlation between Serum OSM and HOMA-IR

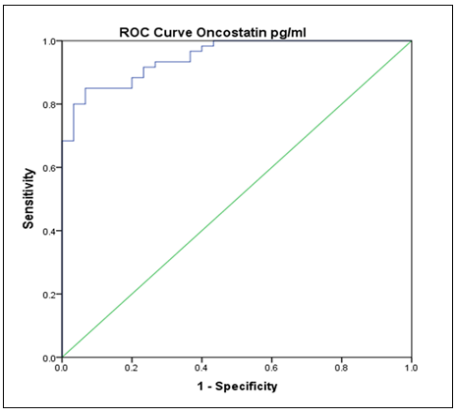

Figure 3. ROC Curve Analysis of Serum OSM for Breast Cancer Detection

Table 3. Correlation between Serum Oncostatin and Studied Parameters in Breast Cancer Women Group

Parameters	r	p-value
Age (years)	0.335	0.001
BMI (kg/m²)	0.223	0.01
ALT (IU/L)	0.675*	0.001
AST (IU/L)	0.693*	0.001
ALP (IU/L)	0.57	0.001
FBG (mg/dL)	0.453	0.001
Insulin (μIU/mL)	0.721*	0.0001
HOMA-IR	0.733*	0.0001
HOMA-β	-0.142	0.068
HOMA-S (%)	-0.592	0.001

r: Pearson correlation coefficient

Table 4. Receiver Operating Characteristic-Area Under Curve Analysis of the Measured Biomarker in BC Patients

Variable	Cut-off concentration	Sensitivity %	Specificity %	AUC	95% CI of AUC	p-value
Oncostatin (pg/mL)	99.46	89.7	84.3	0.927	0.887-0.958	0.001

definitive causality between Oncostatin M (OSM) and breast cancer progression. Additionally, the sample size (n=180), while statistically significant based on pilot data, lacked an a priori power calculation and focused on a localized Iraqi population. The biochemical nature of the study also meant that molecular subtyping of tumors was not performed. Furthermore, the identified OSM cut-off (99.46 pg/mL) remains preliminary and requires external validation in independent cohorts.

Future research should employ longitudinal designs with larger, diverse populations to monitor OSM fluctuations across different treatment phases, such as chemotherapy and radiotherapy. Mechanistic investigations are also warranted to explore the OSM/Insulin axis as a potential pathway. Integrating these findings into personalized immunometabolic screening protocols could refine the role of OSM as a robust progression biomarker in clinical practice.

In conclusion, this study demonstrates that serum Oncostatin M (OSM) and insulin levels are significantly elevated in Iraqi women with breast cancer, highlighting a robust metabolic-inflammatory axis in disease progression. The significant correlation between OSM levels and advanced clinical stages (I–IV) suggests its role as a key biomarker for disease progression and potential metastasis. While biopsy remains the diagnostic gold standard, integrating OSM measurement into clinical protocols alongside CA 15-3 could enhance the monitoring of progression. These findings position the OSM/Insulin axis as a preliminary prognostic indicator and a potential pathway for future therapeutic investigation, pending further longitudinal validation.

Funding

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Clinical trial registration

Not applicable.

Conflicts of interest/Competing interests

Authors declare that they have no conflicts of interest.

Availability of data and material

The data sets used and/or analyzed during the current study are available from the corresponding authors per reasonable request.

Authors' contributions

Hanaa Addai Ali contributed to the conception, design, and final drafting of the manuscript. Hussein Naeem Abd AL-HILFI contributed to data collection and the primary drafting of the manuscript. Hanaa Addai Ali supervised the study. All authors approved the final version for submission.

Ethics approval

This study was approved by the Institutional Review Board (IRB) of the College of Medicine, University of Kufa (Approval No. MEC 133; 10/04/2025). The research followed the 1964 Declaration of Helsinki and its later amendments.

Consent to participate

After being briefed on study objectives and procedures, all participants provided both written and verbal informed consent before sample collection.

Consent for publication

Written informed consent was obtained from all participants for the publication of their de-identified clinical and biochemical data.

Originality Declaration for Figures

All figures included in this manuscript are original and have been created by the authors specifically for the purposes of this study. No previously published or copyrighted images have been used.

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