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Serum Levels of SDF-1 and CXCR4 in Breast Cancer: Correlation with Disease Progression and Chemotherapy Response in Iraqi Women.

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Abstract

Breast cancer is the most frequently diagnosed cancer among women worldwide and remains a significant global health issue. Autophagy plays a dual role in breast cancer, influencing both anti-tumor immunity and tumor progression. This study aimed to investigate the role of autophagy markers, specifically SDF1 and CXCR4, in breast cancer pathogenesis among Iraqi women. A total of 90 participants, aged 25–65 years, were divided into three groups: 30 newly diagnosed breast cancer patients, 30 patients undergoing chemotherapy, and 30 healthy controls. The chemotherapy regimen for the treated group included Adriamycin (60 mg/m^2) combined with cyclophosphamide, administered in 21-day cycles. Diagnosis was confirmed through mammography and histopathological examination. Blood samples (3 ml) were collected, processed, and stored for analysis, with serum levels of SDF1 and CXCR4 measured using ELISA kits. The study revealed that SDF1 levels were significantly elevated in newly diagnosed patients (84.91 $\pm$ 4.2 pg/ml) compared to chemotherapy patients (59.94 $\pm$ 2.18 pg/ml) and controls (57.00 $\pm$ 3.47 pg/ml), with p$\leq$0.001. Similarly, CXCR4 levels were highest in newly diagnosed patients (0.5 $\pm$ 0.06 ng/ml), followed by controls (0.11 $\pm$ 0.01 ng/ml) and chemotherapy patients (0.08 $\pm$ 0.01 ng/ml), also with p$\leq$0.001. A moderate positive correlation between SDF1 and CXCR4 (r = 0.5, p = 0.001) was observed, indicating their potential role in breast cancer progression. These findings highlight the significance of SDF1 and CXCR4 as potential markers for understanding breast cancer pathogenesis and progression, offering insights for targeted therapeutic approaches.

1. Introduction:

Breast cancer is a major health challenge worldwide and is characterized by the uncontrolled proliferation of abnormal cells in breast tissue. Recent studies have highlighted the disease's various biological and treatment-related aspects and emphasized its prevalence in different demographic groups [1]. In Iraq, breast cancer remains the most commonly diagnosed malignancy in women, highlighting the urgent need for effective strategies to understand and treat this disease [2]. It is estimated that approximately 25% of women will be diagnosed with breast cancer during their lifetime [3], and the early onset of the disease in Iraqi women may be due to the socio-political upheavals of the early 21st century [4], [5].

The rate of neoplastic cell proliferation is a crucial factor in predicting cancer prognosis and determining treatment strategies [6]. Studies on breast cancer heterogeneity have uncovered various genetic alterations and signaling pathways that promote tumor growth and progression [7]. Advances in

targeted therapies focusing on hormone receptors and HER2 have significantly improved treatment outcomes for certain breast cancer subtypes, leading to higher survival rates and better quality of life for patients [8]. In addition, research into the tumor microenvironment and the immune response has paved the way for the development of immunotherapies that use the immune system to target malignant cells more effectively [9].

Autophagy plays a multifaceted role in immunity against breast cancer and influences both the anti-tumor immune response and tumor progression. Within the tumor microenvironment, autophagy regulates immune cell function and maintains immune homeostasis [10]. By facilitating the clearance of damaged organelles and proteins in immune cells, autophagy enhances their effector functions, such as antigen presentation and cytokine production [11]. However, deregulated autophagy can allow evasion of the immune system, impair immune surveillance and promote tumor cell survival [12]. Targeting autophagy has emerged as a promising therapeutic strategy to enhance the immune response and improve treatment outcomes. Preclinical studies suggest that inhibiting autophagy may improve the efficacy of immunotherapy by promoting the infiltration and activation of immune cells in the tumor microenvironment [13].

CXCR4 (C-X-C chemokine receptor type 4) is a key receptor involved in the progression and metastasis of breast cancer. It mediates the migration of cancer cells to distant organs by binding to its ligand CXCL12, which is highly expressed in various breast cancer cells. Increased expression of CXCR4 has been associated with poor prognosis, increased metastatic potential and decreased survival. Inhibition of CXCR4 has been shown to reduce the spread of metastases and increase the sensitivity of cancer cells to chemotherapy [14]. Research by [15] has shown that CXCR4 blockade in combination with standard chemotherapy effectively targets primary tumors and inhibits metastasis, leading to better treatment outcomes for patients. Ongoing clinical trials are investigating the therapeutic benefit of such combination therapies in breast cancer [16].

SDF-1, also known as CXCL12, is crucial for the progression and metastasis of breast cancer. It promotes cell survival, proliferation and migration through its interaction with CXCR4 [17]. The CXCL12/CXCR4 axis has been shown to regulate autophagy in breast cancer, supporting cell survival under stress conditions such as chemotherapy resistance. For example, the cytotoxic effects of adriamycin and cyclophosphamide, which trigger apoptosis and DNA damage, can be halted by autophagy triggered by CXCL12/CXCR4 signaling [18].

The interaction of disease stage, grade, patient age, and hormone status significantly influences the prognosis of breast cancer and the response to treatment. Higher expression levels of CXCL12 and CXCR4 are often associated with advanced stages of disease, which favors metastasis and correlates with poorer treatment outcomes. Younger women often have more aggressive forms of breast cancer, which may be related to increased CXCL12 and CXCR4 expression. In addition, hormonal fluctuations may modulate the expression of these markers and enhance interactions between cancer cells and the tumor microenvironment, promoting tumor growth and metastatic potential [19].

Based on these findings, this study hypothesizes that SDF-1 and CXCR4 play a crucial role in the development of breast cancer. Their involvement in tumor cell proliferation and metastasis suggests that they may serve as important biomarkers of disease progression and response to treatment. This study aims to evaluate the expression of SDF-1 and CXCR4 in breast cancer patients and to investigate their association with disease stage, patient age, hormonal status, and mechanisms of action of relevant therapeutics. By elucidating these relationships, we hope to gain valuable insights that could improve diagnostic and therapeutic strategies and ultimately improve patient outcomes. The increasing recognition of the role of autophagy in tumorigenesis has led to the identification of new autophagy-related markers that may serve as prognostic indicators [20], [21]. Early detection of breast cancer is associated with a better prognosis and higher survival rates [22].

2. Materials and Methods:

2.1 Study Design and Setting:

A pilot study was conducted on a sample of Iraqi women who had been diagnosed with breast cancer and attended the Iraqi Medical City (Oncology Teaching Hospital) in Baghdad from August 2023 to December 2023. A total of 90 blood samples were taken, 60 samples from patients and 30 samples from healthy women who served as a control group.

2.2 Population Description:

Patients were selected on the basis of diagnoses made by oncologists and confirmed by mammography and histopathologic findings. The patient group consisted of 30 newly diagnosed women and 30 women undergoing chemotherapy. The participants were between 25 and 65 years old. Exclusion criteria included other cancers, autoimmune diseases, infectious diseases, pregnancy, breastfeeding and any severe acute or chronic illnesses.

2.3 Sample Collection:

Venous blood samples (3 mL) were taken from each patient and the control group. The blood was placed in a gel separation tube. It was then centrifuged at 3000 rpm for 10 minutes. The serum samples were transferred to small plastic tubes and stored at -20^{o}C until further use.

2.4 Laboratory Analysis:

To measure the concentrations of SDF1 and CXCR4 in the samples, a "Double Antibody Sandwich" ELISA kit from ELISA Kits, USNF, USA was used. The optical densities (O.D.) of the samples were compared with a pre-calculated standard curve. The accuracy of the results was ensured by preparing all standards, samples and reagents according to the instructions in the kit brochure

2.5 Laboratory Plasticware and Glassware:

Plasticware and glassware used in this study include single and multichannel pipettes, pipette tips, microcentrifuge tubes, 10 mL vacuum gel tubes, plain tubes, racks, 1.5 mL microcentrifuge tubes, Microcentrifuge tube racks, absorbent papers, 1000 mL graduated cylinders, beakers, conical flasks, 10 mL disposable syringes, tourniquets, wooden applicator sticks, gloves and wash solution containers. These items were sourced from various manufacturers in different countries, including Japan, India, Jordan, Canada, the United Arab Emirates, China, Thailand and Iraq. The pipettes and tips as well as the microcentrifuge tubes, for example, were supplied by Waston Biolab from Japan, while other materials such as the microcentrifuge tubes and racks were sourced from Abdos Labtech in India.

2.6 Equipment:

The equipment used in this study includes a centrifuge, a horizontal freezer, an incubator, a vortex mixer, an ELISA microplate washer, an ELISA microplate reader, a microwave (TOP-wave) and an atomic absorption spectrometer. These devices were purchased from well-known manufacturers, such as Hettich ©(Germany) for the centrifuge, Memmert ©(Germany) for the incubator and BioTek ©(USA) for the ELISA microplate washer and reader. Other instruments, such as the atomic absorption spectrometer and the microwave, were supplied by Analytik Jena, Germany.

2.7 Kits:

Two ELISA kits were used to measure the biomarkers in this study. The first is the Stromal Cell-Derived Factor 1 (SDF1) kit, catalog number SEA122Hu, manufactured by Cloude-clone Corp (USA). The second is the Chemokine C-X-C Motif Receptor 4 (CXCR4) kit, catalog number SEA940Hu, also from Cloude-clone Corp (USA).

2.8 Detection ranges and standard curve concentrations:

The detection range for the SDF1 and CXCR4 tests was between 0.156 and 10 ng/mL. The standard curve concentrations for both biomarkers included: 10 ng/ml, 5 ng/ml, 2.5 ng/ml, 1.25 ng/ml, 0.625 ng/ml, 0.312 ng/ml and 0.156 ng/ml. These concentrations were used to generate standard curves that served as a reference for the quantification of SDF1 and CXCR4 concentrations in patient samples. The standard curve

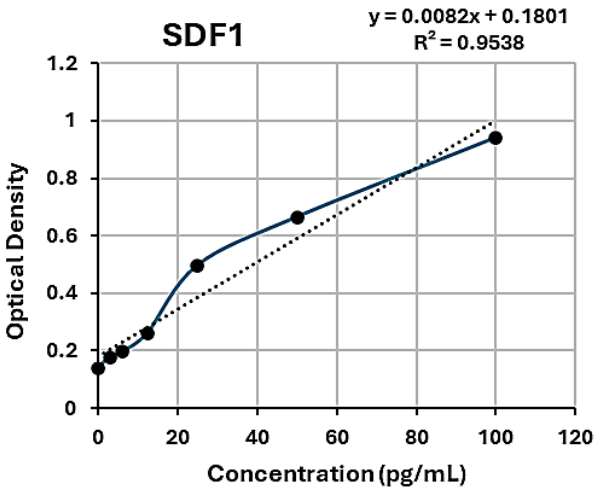

Figure 1. Standard curves of SDF1.

for SDF1, for example, had an R^2 value of 0.9538 as shown in Figure 1, indicating good linearity and accuracy of the measurements. As shown in Figure 2, the standard curve with an R2=0.9919 serves as a reference for the quantification of CXCR4 levels in patient samples.

2.9 Statistical Analysis:

The data was analyzed using SPSS software. The focus was on the evaluation of correlations between biomarkers and other parameters such as cancer stage and grade. The independent T-test and one-way ANOVA were used for comparison. The p-value was determined using the Least Significant Difference (LSD) method, together with Pearson's chi-square test and ROC analysis. Data are presented as mean $\pm$ standard error (S.E.), with a p-value of less than 0.05 considered statistically significant.

3. Results:

3.1 Demographic, Clinical, and Pathological Characteristics:

The study cohort was divided into three groups: newly diagnosed breast cancer patients, patients currently undergoing treatment and a control group, with each group consisting of 30 participants, representing 33.33% of the total sample. Demographic and clinical characteristics such as age, cancer stage and hormone receptor status were analyzed to provide context for the laboratory results. In terms of age distribution, 10 patients (16.67%) were over 50 years old, while the remaining 50 patients (83.33%) were 50 years old or younger. In terms of TNM stage, 8 patients (13.33%) were stage I, 44 patients (73.33%) were stage II, 5 patients (8.33%) were stage III and 3 patients (5%) were stage IV. In terms of tumor grade,

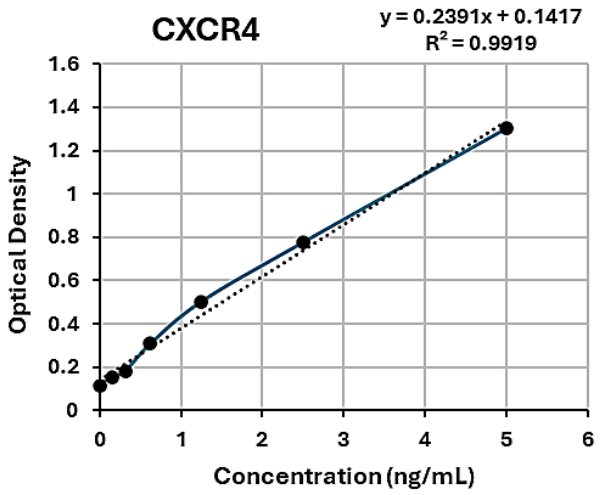

Figure 2. Standard curves of CXCR4.

6 patients (10%) were grade I, 35 patients (58.33%) were grade II and 19 patients (31.66%) were grade III.

3.2 Comparison of the Parameters between the Study Groups:

The data presented in Table 1 show that the SDF1 level increased significantly in newly diagnosed breast cancer patients with a mean concentration of 84.91 ± 4.2 pg/ml, followed by a slightly lower value in patients undergoing treatment (59.94 ± 2.18 pg/ml). In contrast, the control group also had the lowest concentration at 59.94 ± 2.18 pg/ml. Highly significant differences in SDF1 levels were observed between all three groups and between newly diagnosed and treated patients, with p-values < 0.001. Similarly, the highest CXCR4 levels were observed in the newly diagnosed BC patients (0.5 ± 0.06 ng/ml), while the control group had a lower level of 0.11 ± 0.01 ng/ml. The lowest CXCR4 concentration was found in undertreated patients (0.08 ± 0.01 ng/mL). Again, highly significant differences in CXCR4 levels were found between the three study groups and between newly diagnosed and treated patients, with p-values < 0.001.

3.3 Comparison of Parameters (SDF1, CXCR4) between Study Groups Based on Age Categories:

As shown in Table 2, SDF1 levels were significantly higher in controls aged > 50 years (62.78 ± 6.81 pg/ml) than those aged ≤ 50 years (54.52 ± 4 pg/ml), with a p-value of <0.001. In newly diagnosed breast cancer patients, SDF1 levels in those aged >50 years (84.27 ± 5.96 pg/ml) slightly lower than those aged ≤ 50 years (85.39 ± 5.99 pg/ml), although this difference was not statistically significant (p-value = 0.87). Similarly, SDF1 levels were slightly lower in under-treated patients aged > 50 years (58.28 ± 3.74 pg/ml) than in patients aged ≤ 50 years (61.05 ± 2.71 pg/ml), but this difference was also not statistically significant (p-value = 0.7).

Regarding CXCR4 levels, the data in Table 2 show a significant increase in controls aged ≤ 50 years (0.12 ± 0.01 ng/mL) compared to those aged > 50 years (0.09 ± 0,02 ng/mL), with a p-value of < 0.001. In newly diagnosed patients, CXCR4 levels were slightly higher in those aged ¿50 years (0.51 ± 0.08 ng/mL) compared to those aged $\leq$50 years (0.48 ± 0.07 ng/mL), but this difference was not statistically significant (p-value = 0.71). In addition, CXCR4 levels were slightly lower in the undertreated patients aged > 50 years (0.07 ± 0.01 ng/mL) compared to those aged ≤ 50 years (0.09 ± 0.01 ng/mL), although this difference was not statistically significant (p-value = 0.76).

3.4 Comparison of Parameters (SDF1, CXCR4) between Study Groups Based on Grade:

Table 3 shows that there was no significant difference in SDF1 levels between newly diagnosed breast cancer patients based on tumor grade (p-value = 0.27). The highest SDF1 levels were observed in patients with grade II (90.11 ± 5.64 pg/ml), followed by those with grade I (77.30 ± 7.60 pg/ml), and the lowest levels were found in patients with grade III (74.25 ± 8.04 pg/ml). Furthermore, there was no significant difference in SDF1 levels between those with grade III (61.56 ± 2.64 pg/mL) and those with grade II (58.53 ± 3.42 pg/mL) in the under-treated patients, with a p-value of 0.5. A significant difference in SDF1 levels was observed between newly diagnosed patients with grade II and undertreated patients with the same grade (p-value < 0.001), while no significant difference was observed between newly diagnosed and under-treated patients with grade III (p-value = 0.06). As for CXCR4 levels, Table 3 shows that there was no significant difference between newly diagnosed BC patients based on tumor grade (p-value = 0.76 > 0.05). The highest CXCR4 levels were found in patients with grade II (0.52 ± 0.08 ng/ml), followed by those with grade I (0.50 ± 0.11 ng/ml), and the lowest levels were observed in patients with grade III (0.40 ± 0.13 ng/ml). In the under-treated patients, there was no significant difference in CXCR4 levels between those with grade II (0.07 ± 0.01 ng/mL) and those with grade III (0.09 ± 0.01 ng/mL), with a p-value of 0.19. However, a significant difference in CXCR4 levels was found between newly diagnosed patients with grade II and under-treated patients with the same grade (p-value < 0.001), while there was no significant difference in CXCR4 levels in patients with grade III (p-value = 0.07, not significant). In addition, no significant difference in CXCR4 levels was found between under-treated grade II and grade III patients (p-value = 0.19, not significant).

3.5 Comparison of the Parameters (SDF1, CXCR4) between the Study Groups Based on the Stages:

Table 4 shows that SDF1 levels were slightly higher in newly diagnosed stage I breast cancer patients (86.54 ± 4.23

Table 1. Comparison of SDF1 (pg/ml) / CXCR4 (ng/ml) levels between the study groups.

Parameter	Groups	Concentration (Mean ± S.E.)	P value
SDF1 (pg/mL)	Control	57.00 ± 3.47	
	newly diagnosed patients	84.91 ± 4.20a	<0.001**
	Undertreated patients	59.94 ± 2.18	
	Between newly and undertreated patients	-	<0.001**
CXCR4 (ng/mL)	Control	0.11 ± 0.01	
	newly diagnosed patients	0.50 ± 0.06a	< 0.001 **
	undertreated patients	0.08 ± 0.01	
	Between newly and undertreated patients	-	<0.001 **

Table 2. Comparison of SDF1 (pg/ml) / CXCR4 (ng/ml) Levels between the Study Groups Based on Age Categories.

Parameter	Groups	Age groups (years)	Concentration (Mean ± S.E.)	P value
SDF1 (pg/mL)	Control	≤50 (n=20)	54.52 ± 4.00	<0.001**
		>50 (n=10)	62.78 ± 6.81	
	newly diagnosed patients	≤ 50 (n=17)	85.39 ± 5.99 [ab]	0.87 NS
		>50 (n=13)	84.27 ± 5.96 [ab]	
	undertreated patients	≤ 50 (n=18)	61.05 ± 2.71	0.7 NS
		>50 (n=12)	58.28 ± 3.74	
CXCR4 (ng/mL)	Control	≤ 50 (n=20)	0.12 ± 0.01	<0.001**
		>50 (n=10)	0.09 ± 0.02	
	newly diagnosed patients	≤ 50 (n=17)	0.51 ± 0.08 [ab]	0.71 NS
		>50 (n=13)	0.48 ± 0.07 [ab]	
	undertreated patients	≤50 (n=18)	0.09 ± 0.01	0.76 NS
		> 50 (n=12)	0.07 ± 0.01	

[a] vs. control < 50, [b] vs. control > 50.

pg/ml) than those in stage II (84.50 ± 5.17 pg/ml), but this difference was not statistically significant (p-value = 0.85). In addition, there was no significant difference in SDF1 levels in the undertreated patients based on cancer stages (p-value = 0.7). The highest SDF1 level in the undertreated patients was observed in those with stage III (64.21 ± 6.48 pg/ml), followed by stage II (59.56 ± 2.51 pg/ml), and the lowest level was in patients with stage I (55.98 ± 4.82 pg/ml). A significant difference in SDF1 levels was observed between newly diagnosed stage II patients and those undertreated patients with the same stage (p-value < 0.001), while a marginal difference was observed between newly diagnosed and stage I undertreated patients with a p-value of 0.09. Regarding CXCR4 levels, among the newly diagnosed BC patients, those in stage I (0.57 ± 0.09 ng/ml) had higher CXCR4 levels than those in stage II (0.48 ± 0.07 ng/ml), but this difference was not statistically significant (p-value = 0.2). There was also no significant difference in CXCR4 levels among undertreated patients based on stages (p-value = 0.4). The highest CXCR4 level among the undertreated patients was found in stage I patients (0.10 ± 0.02 ng/mL), followed by stage II (0.08 ± 0.01 ng/mL), and the lowest level was observed in stage III patients (0.08 ± 0.02 ng/mL). A significant difference in CXCR4 levels was observed between newly diagnosed stage II patients and undertreated patients at the same stage (p-value < 0.001) and between newly diagnosed and stage I undertreated patients (p-value = 0.03).

3.6 Comparison of Parameters (SDF1, CXCR4) amon -g Study Groups Based on Hormone Receptor Status:

Table 5 indicates that there was no significant difference in SDF1 levels among newly diagnosed breast cancer (BC) patients based on their hormonal receptor status (p-value = 0.35). The highest SDF1 level was observed in patients with ER-, PR-, HER2- (101.85 ± 17.28 pg/mL), followed by those with ER+, PR+, HER2+ (93.19 ± 8.62 pg/mL), and the lowest level was found in patients with ER+, PR+, HER2- (82.98 ± 8.18 pg/mL). Similarly, no significant difference in SDF1 levels was noted among under-treatment patients based on

Table 3. Comparison of SDF1 (pg/ml) L CXCR4 (ng/ml) Levels between Study Groups Based on Grade.

Parameter	Patients' groups	Grade groups	Concentration (Mean ± S.E.)	P value
SDF1 (pg/mL)	newly diagnosed patients	I (n=6)	77.30 ± 7.60	0.27 NS
		II (n=19)	90.11 ± 5.64	
		III (n=5)	74.25 ± 8.04	
	undertreated patients	II (n=16)	58.53 ± 3.42	0.5 NS
		III (n=14)	61.56 ± 2.64	
	Between early & undertreated patients	II	-	< 0.001 **
	Between newly & undertreated patients	III	-	0.06 NS
CXCR4 (ng/mL)	newly diagnosed patients	I	0.50 ± 0.11	0.76 NS
		II	0.52 ± 0.08	
		III	0.40 ± 0.13	
	undertreated patients	II	0.07 ± 0.01	0.19 NS
		III	0.09 ± 0.01	
	Between newly & undertreated patients	II	-	<0.001**
	Between newly & undertreated patients	III	-	0.07 NS

their hormonal status (p-value = 0.61). The highest level was found in patients with ER+, PR-, HER2- (63.62 ± 7.75 pg/mL), followed by those with ER-, PR-, HER2+ (62.41 ± 3.29 pg/mL), and the lowest level was observed in patients with ER+, PR+, HER2- (58.26 ± 2.87 pg/mL). No significant differences in CXCR4 levels were found between newly diagnosed BC patients based on hormone receptor status (p-value = 0.31). The highest CXCR4 level was observed in patients with ER+, PR+, HER2+ (0.75 ± 0.06 ng/ml), followed by those with ER-, PR-, HER2+ (0.54 ± 0.23 ng/ml), and the lowest level was observed in patients with ER-, PR-, HER2- (0.26 ± 0.13 ng/ml). Similarly, no significant difference in CXCR4 levels was found in under-treated patients depending on hormone status (p-value = 0.28). The highest CXCR4 level was observed in patients with ER-, PR-, HER2+ (0.10 ± 0.01 ng/mL), followed by those with ER+, PR+, HER2- (0.08 ± 0.01 ng/mL), and the lowest level was observed in patients with ER+, PR-, HER2- (0.05 ± 0.02 ng/mL).

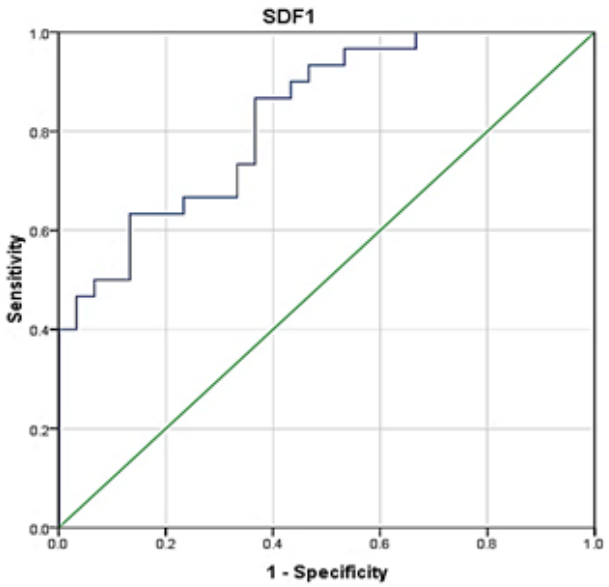

Figure 3. SDF1 ROC Curve.

3.7 Receiver Operating Characteristic (ROC) Test of Variables:

As shown in Table 6, there was a significant moderate positive correlation between the SDF1 and CXCR4 levels (r = 0.5, P = 0.001). As shown in Figure 3, the results indicate that the AUC for SDF1 is remarkably high at 0.83, with a statistically significant difference (p-value < 0.001). The sensitivity for SDF1 is 63% and the specificity is 87%, with a cutoff value of 76.07, indicating that SDF1 is a good predictor for breast cancer patients. In addition, the AUC for CXCR4 is even higher at 0.94, with a significant p-value of less than 0.001. CXCR4 has a sensitivity of 77% and a perfect specificity of 100%, with a cutoff value of 0.221, making it an excellent predictor of breast cancer, as shown in Figure 4. The ROC curve summary for the parameters is as follows:

- **SDF1**: AUC = 0.83, Cutoff = 76.07, Sensitivity = 63%, Specificity = 87%, p-value < 0.001
- **CXCR4**: AUC = 0.94, Cutoff = 0.221, Sensitivity = 77%, Specificity = 100%, p-value < 0.001

4. Comparative Analysis of Laboratory Results:

4.1 Comparison of SDF1 and CXCR4 Levels:

The comparative analysis of laboratory results focused on the assessment of SDF1 and CXCR4 levels between newly

Table 4. Comparison of SDF1 (pg/ml) / CXCR4 (ng/ml) Levels between the Study Groups Based on the Stages.

Parameter	Patients' groups	Stage groups	Concentration (Mean ± S.E.)	P value
SDF1 (pg/mL)	newly diagnosed patients	I (6)	86.54 ± 4.23	
		II (24)	84.50 ± 5.17	
	undertreated patients	I (2)	55.98 ± 4.82	
		II (24)	59.56 ± 2.51	0.7 NS
		III (4)	64.21 ± 6.48	
	Between newly & undertreated patients	I	-	0.009 **
	Between newly & undertreated patients	II	-	< 0.001**
CXCR4 (ng/mL)	newly diagnosed patients	I (6)	0.57 ± 0.09	0.56 NS
		II (24)	0.48 ± 0.07	
	Treated patients	I (2)	0.10 ± 0.02	0.9 NS
		II (24)	0.08 ± 0.01	
		III (4)	0.08 ± 0.02	
	Between newly & undertreated patients	I	-	0.03 *
	Between newly & undertreated patients	II	-	<0.001**

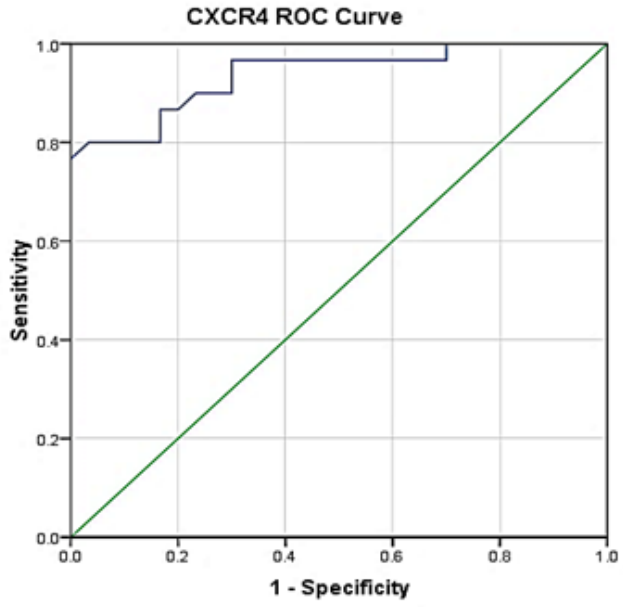

Figure 4. CXCR4 ROC Curve.

diagnosed breast cancer patients and those currently undertreated patients. The results showed a significant difference between the two groups. Newly diagnosed patients had a mean SDF1 level of 84.91 ± 4.20 pg/ml, which was significantly higher than under-treated patients, whose SDF1 level was 59.94 ± 2.18 pg/ml, with a p-value of ¡ 0.001. CXCR4 levels were also significantly higher in the newly diagnosed patients (0.50 ± 0.06 ng/ml) than in the undertreated patients (0.08 ± 0.01 ng/ml), with a p-value of ¡ 0.001. This indicates a significant difference in laboratory markers between the two patient groups.

4.2 Association with Prognosis and Tumor Behavior:

To determine whether these markers are associated with poor prognosis or aggressive tumor characteristics, we performed a correlation analysis with tumor grade and stage.

Findings:

•SDF1:

Higher SDF1 levels were observed in patients with early-stage disease (stage I and II) compared to patients with advanced-stage disease (stage III and IV), indicating a potential association with less aggressive tumors.

•CXCR4:

Elevated CXCR4 levels correlated with higher tumor grades, suggesting that this marker may be associated with more aggressive tumor behavior and a poorer prognosis.

This analysis shows significant differences in SDF1 and CXCR4 levels between newly diagnosed and undertreated patients, with both markers showing a potential association with tumor aggressiveness. Further research is needed to investigate their role in predicting treatment outcomes in breast cancer patients.

Table 5. Comparison of SDF1 (pg/mL) / CXCR4 (ng/mL) Levels between Study Groups Based on Hormonal Status.

Parameter	Patients' groups	Hormonal status groups	Concentration (Mean ± S.E.)	P value
SDF1 (pg/mL)	newly diagnosed patients	ER+, PR+, HER2-	82.98 ± 8.18	0.35 NS
		ER+, PR-, HER2-	87.55 ± 3.90	
		ER-, PR-, HER2+	69.58 ± 6.88	
		ER+, PR+, HER2+	93.19 ± 8.62	
		ER-, PR-, HER2-	101.85 ± 17.28	
	undertreated patients	ER+, PR+, HER2-	58.26 ± 2.87	0.61 NS
		ER+, PR-, HER2-	63.62 ± 7.75	
		ER-, PR-, HER2+	62.41 ± 3.29	
CXCR4 (ng/mL)	newly diagnosed patients	ER+, PR+, HER2-	0.44 ± 0.09	0.31 NS
		ER+, PR-, HER2-	0.52 ± 0.07	
		ER-, PR-, HER2+	0.54 ± 0.23	
		ER+, PR+, HER2+	0.75 ± 0.06	
		ER-, PR-, HER2-	0.26 ± 0.13 [a]	
	undertreated patients	ER+, PR+, HER2-	0.08 ± 0.01	0.28 NS
		ER+, PR-, HER2-	0.05 ± 0.02	
		ER-, PR-, HER2+	0.10 ± 0.01	

[a] vs. in newly group ER+, PR+, HER2

Table 6. The Correlation between the variables.

	Parameter	SDF1	CXCR4
SDF1	Pearson Correlation	1	
	Sig. (2-tailed)		
CXCR4	Pearson Correlation	0.460**	1
	Sig. (2-tailed)	0.001	

5. Discussion:

Chemokines are categorized into four subfamilies based on the positioning of cysteine residues in their sequences: CC, CXC, C, and CX3C chemokines. CXCL12 (SDF-1) belongs to the CXC group and is involved in the regulation of leukocyte migration and tissue regeneration. SDF-1 levels are higher in newly diagnosed breast cancer (BC) patients (84.91 ± 4.2 pg/ml) than in under-treated patients (59.94 ± 2.18 pg/ml) and control subjects (59.94 ± 2.18 pg/ml), with significant differences between the groups ($p < 0.001$) [23]. A higher SDF-1 level in BC could help prevent metastasis by interacting with the cancer cells and thus improving the prognosis [24]. A meta-analysis by [25] found that increased SDF-1 expression correlates with poor prognosis in oesophageal cancer, pancreatic cancer and lung cancer, while it is associated with better overall survival in BC. The discrepancy likely results from the different sources of SDF-1 (e.g. tumor vs. stromal cells), with stroma-derived SDF-1 promoting local tumor invasion and tumor cell-derived SDF-1 influencing metastasis. CXCR4, which is overexpressed in BC cells, plays a crucial role in the mobilisation of circulating tumor cells. The binding of SDF-1 to CXCR4 activates processes that are crucial for tumor growth, migration and metastasis [26]. CXCR4 is typically low in normal breast tissue but elevated in BC cells [23], and its signaling pathway, including activation of HER2, enhances invasiveness in various cancers [26]. High CXCR4 expression is associated with poor prognosis in hematological and solid tumors [16], including BC. CXCR4 levels are significantly higher in newly diagnosed BC patients (0.5 ± 0.06 ng/ml) compared to controls (0.11 ± 0.01 ng/ml), with a decrease in under-treated patients (0.08 ± 0.01 ng/ml) [23]. Meta-analyses by Zhang et al. (2014) show that high CXCR4 expression correlates with the spread of cancer to lymph nodes and other metastatic sites and with poorer disease-free survival (DFS) and overall survival (OS) in BC. Increased CXCR4 expression in the whole cell, cytoplasm and nucleus is associated with poorer prognosis, especially in DFS [27]. Thus, CXCR4 serves as a strong prognostic marker in BC. Age is a significant risk factor for developing BC, with incidence increasing after the age of 40, particularly in women over 50 due to accumulated genetic mutations and chromosomal damage [28]. BC is rare in women under the age of 35, but over 80% of cases occur in women aged 50 and over [29] (Al-dulemey, 2022). In this study, 13% of newly diagnosed and treated BC patients were > 50 years old, which is consistent with other reports indicating a high prevalence in women over 50 years of age [28], [30]. However, other studies have found that the highest incidence of BC is in women aged 40-49 years [31], [32], [33]. Younger women with BC tend to have larger tumors, poorer survival and positive lymph nodes [34], although BC is

increasing in younger women worldwide [35]. The histologic grading of BC also influences the prognosis. Grade I tumors have a 10-year survival rate of about 80%, while grade III tumors have a survival rate of 45% [36]. In this study, most patients were diagnosed with grade II tumors (32%), and only 8% had grade III. Similar results were reported by [37], in which 72.9% of patients had grade II and 27.1% had grade III. Other studies by [38] and [28] also found that grade II was most common, followed by grade III. [5] (2020) and [39] also confirmed that grade II was most common, followed by grade III in BC diagnoses. [40] found that in a sample of 50 women diagnosed with breast cancer, tumor grades were distributed as follows: 4% for grade I, 78% for grade II and 18.9% for grade III. Similarly, [41] reported that 48% and 36% of patients had grade I and II tumors respectively.

According to the AJCC/TNM classification system, most patients in this study were diagnosed as stage II (40%) or undertreated stage II (40%), with the lowest proportion being stage I patients (3%). [40] (2022) reported that the majority of their sample was at stage IIA, followed by IIB, IIIA, IIIC and stage IV, with 6% at stage IA and 18% at stage IV. Other studies by [5] and [28] also showed that stage II was the most common, followed by stage III. [38] observed that most patients were diagnosed at stage II, suggesting that the BC was either confined to the breast or had spread to nearby lymph nodes. However, small percentages (0.6%) of women were diagnosed at stage IV. Hormone receptor status has a significant impact on the treatment and survival of BC. Estrogen and progesterone receptor positivity (ER+ and PR+) indicates a favorable response to endocrine therapy [42], [43]. In this study, the majority of under-treated patients were ER+, PR+, HER2- (32%), while the lowest proportion of newly diagnosed patients were ER-, PR-, HER2- (5%). [28] (2021) found that 80% of their cases had positive ER or PR expression, with 60% showing strong positivity. ER-negative tumors generally have poorer outcomes, including early recurrence and lower survival rates.

The HER2/neu receptor is another important marker for BC prognosis. [28] (2021) reported that 23.3% of cases showed HER2-positive staining. Studies from Iraq also indicate variable HER2 expression, with [44] finding 41.3% overexpression in certain regions. [38] showed that 64.8% of women were ER/PR-positive and HER2-negative, with most tumours being more dependent on PR expression. Furthermore, a correlation between cancer stage and hormone receptor status was observed, with triple-negative BC (ER-, PR-, HER2-) occurring more frequently in stage III [45]. These results emphasize the role of hormone receptors and HER2 status in the prognosis and treatment of BC. HER2 overexpression is associated with a poorer prognosis but may also predict a favorable response to certain chemotherapies [42]. In our study, the majority of under-treated patients were ER+ and PR+ (32%), while the smallest proportion of newly diagnosed patients were ER-, PR- and HER2- (5%). These results are consistent with previous studies indicating that ER+ and PR+ tumors generally respond better to hormone therapy and are associated with more favorable outcomes [42]. Conversely, ER-, PR- and HER2-negative tumors, while less common, tend to be more aggressive and are often diagnosed at advanced stages, reflecting the association between the absence of these receptors and increased tumor aggressiveness and poorer prognosis. [28] reported that 80% of cases tested positive for hormone receptors, which is partly in line with our findings, although a lower incidence of HER2 positivity was found in their study. Similarly, [37] in Nasiriyah found that 64.8% of breast cancer cases were ER/PR+ and HER2-positive, which is consistent with our results showing that most under-treated patients were ER/PR-positive but HER2-negative.

Despite minor differences between studies, the importance of assessing hormone receptor status (ER, PR, HER2) as a critical biomarker for treatment decisions and prognosis remains. These receptors are crucial for tumor response to hormonal therapy and chemotherapy. The results of our study are consistent with the existing literature on the distribution of hormone receptor status and stage in breast cancer (BC) patients.

Notably, the majority of undertreated patients in our study were ER+ and PR+ (32%), which is consistent with findings from [28] and [38], where a significant proportion of patients were also ER/PR-positive. [42] suggest that ER+ and PR+ tumors are generally associated with a better response to endocrine therapies and more favorable outcomes, which is supported in this clinical understanding. According to our study, only 5 percent of newly diagnosed patients with triple-negative breast cancer (ER-, PR-, HER2-) have the condition, which is in line with the less common but more aggressive nature of these tumors. [45] reported that triple-negative tumors are often diagnosed at advanced stages and have a lower prognosis, which is consistent with this finding. The presence of triple-negative disease in our study, even though it is rare, emphasizes the significance of early detection and the challenges of managing aggressive BC forms.

Our findings regarding tumor grade also support the literature, with most patients diagnosed at grade II (32%), which aligns with previous studies such as those by [37] and [39], where grade II tumors were most common. The grade of tumor is a crucial factor in predicting survival rates, with higher-grade tumors (grade III) having lower survival rates [36]. In our study, the distribution of tumor grades shows that while there are many patients with moderate-grade tumors, aggressive forms (grade III) are less common and still require clinical management attention.

The percentage of patients diagnosed at stage II in our study is the same as in other regional studies [5], [40]. Patients diagnosed at this stage are typically better off than those

diagnosed at more advanced stages, such as stage IV, due to the presence of localized disease or regional lymph node involvement. The staging data highlights the requirement for enhanced screening and early detection methods to cut down on the occurrence of later-stage diagnoses.

With respect to chemokines, CXCR4 and SDF-1 levels, our study corroborates findings by [23] and [46], showing higher SDF-1 in newly diagnosed BC patients (84.91 ± 4.2 pg/mL), compared to those undertreated patients (59.94 ± 2.18 pg/mL). SDF-1 levels that are higher are linked to better outcomes in BC, as it works by preventing metastasis by interfering with cancer cells [24]. However, there remains some contradiction in the literature, where elevated SDF-1 expression has also been linked to poor prognosis in other cancers [25], [47]. The differences may have to do with the different sources of SDF-1 (tumor and stromal cells), where stromal-derived SDF-1 promotes local tumor invasion, while tumor-derived SDF-1 may affect metastasis.

Similarly, the high expression of CXCR4 in BC patients, especially in newly diagnosed cases (0.5 ± 0.06 ng/mL), as compared to controls (0.11 ± 0.01 ng/mL), suggests a critical role for CXCR4 in cancer progression and metastasis. This is in line with [26] which shows that SDF-1 activates CXCR4 and leads to the migration and invasion of tumor cells. The use of CXCR4 as a prognostic marker is supported by the elevated expression in our cohort, which has been linked to poor prognosis and metastatic spread [27].

6. Conclusion:

The current study parameters recorded a significant increase in patients (newly and undertreated) versus control, also the statistical analysis revealed a significant impact of some clinical characteristics of patients of the serum level of the studied parameters. Breast cancer is affected by both innate and adaptive immunity through CXCL12/CXCR4 signaling. For example, it induces the transformation of monocytes into tumor-supporting TAMs and promotes immunosuppression via Tregs recruitment. Furthermore, CXCL12 influences stromal cells and directs the transformation of normal fibroblasts into CAFs, which also release CXCL12 and contribute to tumor development. Finally, the CXCL12/CXCR4 signaling induces breast cancer cell motility and is involved in all types of breast cancer metastasis. Our results highlighted the potential role of SDF-1, CXCR4, and CXCR7 in acquiring the malignant phenotype of tumor cells in breast cancer. They may constitute a potential therapeutic target in the aggressive form of the disease, so according to this finding, we conclude that (SDF1, and CXCR4) may be effective therapeutic targets to halt disease progression.

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مستويات $SDF-1$ و $CXCR4$ في مصل سرطان الثدي: الارتباط بتطور المرض واستجابة العلاج الكيميائي لدى النساء العراقيات

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الخلاصة

سرطان الثدي هو أكثر أنواع السرطان شيوعاً بين النساء على مستوى العالم ويُعدّ مشكلة صحية عالمية كبيرة. يلعب الالتهام الذاتي دوراً مزدوجاً في سرطان الثدي، حيث يؤثر على المناعة المضادة للأورام وتطور الورم. هدفت هذه الدراسة إلى استكشاف دور مؤشرات الالتهام الذاتي، تحديداً *SDF1* و *CXCR4* ، في مسببات سرطان الثدي بين النساء العراقيات. شملت الدراسة 90 مشاركة تتراوح أعمارهن بين 25 و 65 عاماً، قُسمن إلى ثلاث مجموعات: 30 مريضة تم تشخيصهن حديثاً بسرطان الثدي، 30 مريضة يخضعن للعلاج الكيميائي، و 30 شخصاً من الأصحاء كعينة ضابطة. تضمن نظام العلاج الكيميائي للمجموعة المعالجة *Adriamycin* (60 ملغم / م ^{2}) بالتزامن مع *Cyclophosphamide* ، حيث أُعطي العلاج على دورات كل 21 يوماً. تم تأكيد التشخيص باستخدام تصوير الثدي الشعاعي والفحص النسيجي. جُمعت عينات دم (3 مل) من المشاركات، وتمت معالجتها وتخزينها لتحليل مستويات *SDF1* و *CXCR4* في المصل باستخدام *ELISA* . أظهرت النتائج أن مستويات *SDF1* كانت مرتفعة بشكل ملحوظ لدى المريضات حديثات التشخيص (84.91 ± 4.2 بيكوغرام مقارنة بالمريضات الخاضعات للعلاج الكيميائي (59.94 ± 2.18 بيكوغرام / مل) والعينة الضابطة (57.00 ± 3.47 بيكوغرام / مل)، مع دلالة إحصائية ($p \leq 0.001$). بالمثل، كانت مستويات *CXCR4* الأعلى لدى المريضات حديثات التشخيص (0.5 ± 0.06 نانوغرام / مل)، يليها الأصحاء (0.11 ± 0.01 نانوغرام / مل)، وكانت الأدنى لدى المريضات الخاضعات للعلاج الكيميائي (0.08 ± 0.01 نانوغرام / مل)، أيضاً بدلالة ($p \leq 0.001$). لوحظت علاقة ارتباط إيجابية معتدلة بين *SDF1* و *CXCR4* ($r = 0.5$ ، $p = 0.001$). تُبرز النتائج أهمية *SDF1* و *CXCR4* كمؤشرات لفهم مسببات سرطان الثدي وتطوره، مما يفتح آفاقاً لاستراتيجيات علاجية مستهدفة

الكلمات الدالة : الورم؛ الاستجابات المناعية؛ الانتقال؛ العلاج الكيميائي.

التمويل: لايوجد.

بيان توفر البيانات: جميع البيانات الداعمة لنتائج الدراسة المقدمة يمكن طلبها من المؤلف المسؤول.

اقرارات:

تضارب المصالح: يقر المؤلفون أنه ليس لديهم تضارب في المصالح.

الموافقة الأخلاقية: لم يتم نشر المخطوطة أو تقديمها لمجلة أخرى، كما أنها ليست قيد المراجعة.