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Assessment of IL-8 and Some Biochemical Parameters in Breast Cancer Patients Post Chemotherapy

Evan Jawad Salman, Jabbar H. Yenzeel
Department of Biology, College of Science, University of Baghdad, Baghdad, Iraq

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Abstract

Background: One kind of cancer that starts as a proliferation of cells in the breast tissue, frequently developing into tumors, is breast cancer. With notable incidence rates in both industrialized and developing nations, it is the most prevalent cancer diagnosed in women globally. Environmental factors, lifestyle decisions, and hormones all increase the risk of breast cancer. It was demonstrated that individuals with breast cancer had greater levels of a number of pro-inflammatory cytokines, which explains their function in the pathogenicity of the disease and its therapy. The hypothesis of this study includes how chemotherapy for breast cancer affects the level of interleukins.

Objective: This work aimed to investigate the change in the concentration of interleukin-8 and some biochemical parameters in breast cancer Iraqi patients after receiving different doses of chemotherapy.

Materials and Methods: Seventy women diagnosed with breast cancer (35 newly diagnosed do not receive chemotherapy and 35 receiving different doses of chemotherapy) and thirty healthy were enrolled in this study during their attendance at the Oncology Hospital in the Medical City in Baghdad during the period from February 2024 to May 2024. All participants' ages ranged between (30 to70) years. Blood samples were collected from all women to measure the CBC and to evaluate the level of Interleukin- 8, vascular endothelial growth factor (VEGF), total antioxidant capacity (TAC), and C- reactive protein (CRP) level by using (ELISA) technique.

Result: The results of the study expressed as the mean ± SE showed that WBC, RBC, Hb, neutrophil, lymphocytes, monocyte, and platelets highly significant ($P \leq 0.01$) decrease in breast cancer (newly diagnosis and chemotherapy-treated) women in comparison with control. Also, the results showed a highly significant ($P \leq 0.01$) increase in the level of IL-8, VEGF, and CRP in newly diagnosed and chemotherapy-treated breast cancer patients in comparison with the control. While the TAC showed a highly significant ($P \leq 0.01$) decrease in breast cancer patients in comparison with the control. Concerning the number of doses in chemotherapy-treated women, the result showed a significant ($P \leq 0.01$) decrease in CBC except for PLT(NS) in dose (9-20) as compared with dose (5-8) and dose (2-4). Also, the results showed a highly significant ($P \leq 0.01$) decrease in the level of IL-8 and TAC in dose (9-20) as compared with dose (5-8) and dose (2-4). While there was a significant ($P \leq 0.01$) increase in the level of CRP in dose (9-20) as compared to other doses. The level of VEGF showed a non-significant difference between different doses.

Conclusion: It can be concluded that the changes in IL-8 and other biochemical parameters may be a good indicator for assessing the activity of breast cancer for newly diagnosed and chemotherapy-treated women.

Keywords: IL-8, CRP, VEGF, TAC, breast cancer, pro-inflammatory cytokines.

*Email: evan.j@sc.uobaghdad.edu.iq

تقييم البين ابيضاض 8 وبعض المعايير الكيموحيوية لدى مرضى سرطان الثدي بعد تلقي العلاج الكيميائي.

ايفان جواد سلمان ، د.جبار حميد ينزيل

[1]قسم علوم الحياة ، جامعة بغداد، بغداد ، العراق

الخلاصه

سرطان الثدي هو نوع من السرطان يبدأ كنمو للخلايا في أنسجة الثدي، وغالبًا ما يشكل أورامًا وهو أكثر أنواع السرطان شيوعًا بين النساء في جميع أنحاء العالم، مع معدلات حدوث كبيرة في كل من البلدان المتقدمة والأقل نموًا. عوامل الخطورة للإصابة بسرطان الثدي تشمل الهرمونات واختيارات نمط الحياة والمحيط البيئي. لوحظ ان ارتفاع مستوى بعض الحركيات الخلوية الالتهابية في مرضى سرطان الثدي وهذا يفسر الدور الكبير لها في الإمراضية والعلاج. تتضمن فرضية هذه الدراسة هل تؤثر العلاجات الكيميائية لسرطان الثدي على مستوى الإنترلوكينات؟

الهدف من هذا العمل هو التحري عن التغيرات في مستوى البين ابيضاض 8 وبعض المعايير الكيموحيوية لدى مرضى سرطان الثدي بعد تلقي جرعات مختلفة من العلاج الكيميائي.شملت الدراسة سبعون مريضة تم تشخيص إصابتهن بسرطان الثدي (35 منهن مشخصات حديثا ولم يسبق لهن تلقي العلاج الكيميائي و 35 تم اعطائهن جرعات مختلفة من العلاج الكيميائي) . فضلا عن مشاركة ثلاثين امرأه سليمه كمجموعة سيطرة خلال حضورهن الى مستشفى الأورام في مدينة الطب ببغداد خلال الفترة من فبراير 2024 إلى مايو 2024. تراوحت أعمار المشاركات بين (30 إلى 70) عاما . جمعت عينات الدم من جميع المشاركات لقياس صورة الدم و تقييم مستوى البين ابيضاض 8 وبعض المعايير الكيموحيوية مثل السعة الكلية لمضادات الاكسدة والبروتين التفاعلي سي وعامل النمو الوعائي البطاني لدى مرضى سرطان الثدي بعد تلقي جرعات مختلفة من العلاج الكيميائي باستخدام تقنية الممتز المناعي المرتبط بالأنزيم (ELISA).

اظهرت نتائج صورة الدم الكاملة حدوث انخفاض معنوي في العدد الكلي للخلايا البيض والكريات الحمر وتركيز خضاب الدم والخلايا العدلة والقعدة والوحيدة النوى والصفيحات الدموية في مريضات سرطان الثدي المشخصات حديثا واللواتي تلقن العلاج الكيميائي مقارنه بالنساء السليمات. أظهرت النتائج ارتفاعا معنويا عاليا ($P \leq 0.01$) في مستوى البين ابيضاض 8 و عامل النمو البطاني الوعائي والبروتين التفاعلي سي CRP في المريضات المصابات بسرطان الثدي المشخصات حديثًا ومريضات سرطان الثدي المعالجات بالعلاج الكيميائي مقارنة بمجموعات السيطرة, في حين اظهرت السعة الكلية لمضادات الاكسدة انخفاضا معنويا لدى مريضات سرطان الثدي. فيما يتعلق بعدد الجرع لمريضات سرطان الثدي اظهرت النتائج انخفاض معنوي عالي في صورة الدم عدى الصفيحات الدموية في الجرعات 9–20 مقارنة بالجرعات 5–8 و2–4 , كذلك اظهرت النتائج انخفاض معنوي عالي في مستوى البين ابيضاض 8 والسعة الكلية لمضادات الاكسدة في الجرعات من 9–20 مقارنة بباقي الجرع ,في حين حدث ارتفاع معنوي في البروتين التفاعلي سي في نفس الجرعات ولم يلاحظ حدوث تغير معنوي في مستوى عامل النمو البطاني الوعائي بين الجرعات المختلفة .يمكن الاستنتاج بأن التغيرات الحاصلة في مستويات ال IL–8 وباقي المعاير الكيموحيوية قد يكون مؤشرا جيدا لتقييم فعالية العلاج الكيميائي لسرطان الثدي.

Introduction

When the body's cells begin to proliferate uncontrollably, cancers begin. Because metastases spread quickly, some malignancies are discovered at a later stage, making early diagnosis more difficult [1]. The leading cause of cancer-related mortality among women is breast cancer. It is still difficult to prevent breast cancer worldwide since it is a multi-step process that involves several cell types. It is the first of the top ten cancerous tumors that are causing harm to Iraqi citizens. Breast cancer is primarily incurable since it is a metastatic cancer that frequently spreads to distant organs such as the brain, liver, lung, and bone [2]. Sulaymaniyah, an Iraqi governorate, has the highest incidence rate of breast cancer in females between 2006 and 2014, and in 2017, it was shown to be the most common cancer in Basra, Iraq [3].

Early cancer detection is crucial and has a big influence on how the illness is managed in terms of therapy options, reducing toxicity from short- and long-term treatments, extending overall survival, and enhancing patients' quality of life. In order to lower death rates and raise survival rates, it is crucial to investigate the potential of biological changes linked to breast cancer for the creation of precise, effective, and easily accessible diagnostic techniques, particularly in regions with subpar healthcare facilities [4]. Age, gender (female), prior breast cancer, benign breast illness, and genetic factors such as a family history of breast cancer or other cancer types and women with BRCA1 or BRCA2 gene mutations are risk factors for breast cancer [5].

The creation of an immunological milieu that suppresses or compromises antitumor immune responses is one of the most significant ways that cancer promotes its own growth. Many cancer patients who do not react to immunotherapy strategies meant to activate preexisting anticancer immune responses, such as immune checkpoint inhibition, have a cancer tolerant immunological microenvironment [6].

Cytokines are small secreted proteins that are key modulators of inflammation. There are a large number of studies showing that the expression of various cytokines is altered in breast cancer [7]. Interleukin-8, a CXC chemokine, is crucial for controlling the inflammatory response. It has been characterized as a neutrophil chemo-attractant and is crucial for the T-cell-helper type 1 response. Cancer cells have been found to overexpress IL-8, which promotes tumor development, angiogenesis, and metastasis [8].

Although IL-8 has been shown to promote cancer metastasis and development through a variety of pathways, such as pro-angiogenesis and the preservation of cancer stem cells, its capacity to draw in and effectively influence neutrophils and macrophages is perhaps one of the most crucial elements [7]. ER-negative and/or HER2-positive breast cancer can be identified by IL-8. ER and HER2 crosstalk-dependent IL-8 expression may affect the prognosis and prediction of breast cancer. IL-8 expression may rise even though it is inversely correlated with ER state [9].

Since they are the substances that prevent the attack and the development of radical species within cells, antioxidants are the body's first line of defense against free radicals and other oxidants. The total antioxidant status (TAS) refers to the collection of antioxidants within the body. Reactive oxygen species (RNS) and reactive nitrogen species (ROS) both enhance the propensity for tumor cells to spread by contributing in distinct ways to carcinogenesis and the malignant development of tumor cells. Indeed, they are increasingly seen as a trait that distinguishes cancer. These species cause genetic instability and genomic

damage. They also operate as mediators of mutagenic, and survival signals through adhesion molecules and growth factor receptors, which encourage cell mobility and trigger angiogenesis, inflammation, and repair in the tumor microenvironment [10]. Antioxidants reduce the risk of breast cancer by reducing oxidative stress; however, it is still unknown how total antioxidant capacity (TAC) and cancer recurrence are related. TAC is inversely correlated with cancer recurrence and mortality in patients with breast cancer. Dietary TAC was negatively associated with breast cancer risk, particularly in postmenopausal women [11].

Hepatocytes produce C-reactive protein (CRP), an acute-phase reactant inflammatory protein, in reaction to cytokines generated by leucocytes in the tumor microenvironment. Chronically inflammatory breast cancer survivors are susceptible to metabolic abnormalities and recurrence. Patients with breast cancer will live longer if they take CRP-lowering medications in addition to chemotherapy. Additionally, it predicts the likelihood of later cardio toxicity in chemotherapy patients [12]. The benefit of detecting CRP as opposed to other inflammatory cytokines is that the protein levels are significantly greater and stay elevated for longer. The high-sensitivity C-reactive protein (hsCRP) test is more sensitive than the conventional CRP test because it can more precisely identify lower protein quantities [13]. An important part of the pathophysiology of breast cancer involves the VEGF family of proteins and their receptors. It has been demonstrated that these proteins are valuable diagnostic indicators. VEGF proteins may be used as early breast cancer biomarkers, therapy success indicators, and patient survival indicators [14].

Material and methods

Seventy women patients suffering from breast cancer (35 newly diagnosed and do not receive chemotherapy and 35 receiving different doses of chemotherapy), participated in the current study after being diagnosed by a specialized doctor. Also, adjuvant and neoadjuvant chemo drugs and metastatic breast cancer include; Anthracyclines, such as doxorubicin (Adriamycin), Taxanes, such as paclitaxel (Taxol), docetaxel (Taxotere), Capecitabine (Xeloda). Taxanes: Paclitaxel (Taxol), and albumin-bound paclitaxel (Abraxane). Chemo cycles are most often 2 or 3 weeks long. The schedule varies depending on the drugs used; adjuvant and neo adjuvant chemo is often given for a total of 3 to 6 months, depending on the drugs used. The length of treatment for metastatic (Stage 4) breast cancer depends on how well it is working and what side affects you have. In addition, thirty healthy women as control through their attendance at the first oncology hospital in the Medical City in Baghdad during the period from February 2024 to May 2024. The age of all participants' women was ranged from (30-70 years). The required data was collected from all patients after obtaining their permission, based on the ethics of the College of Science, University of Baghdad. Under the reference number (No. CSEC/0924/0061). Blood samples were collected from all participants' women and divided into two parts: the first part was placed in an anticoagulant tube for CBC determination, and the second part was placed in a gel tube and coagulated for 10 minutes at room temperature. Subsequently, the serum separated through centrifugation at a speed of 3000 rpm for 10 minutes. The serum was stored in a deep freezer at-20°C .The levels of IL-8, VEGF, TAC and CRP level were measured based on the Sandwich-ELISA Technique. The procedure was done according to the direction of the manufacturer Bioassay Technology Laboratory Company, (BT Lab), China.

Statistical Analysis

The impact of different groups on study parameters was found using the Statistical Analysis System-SAS (2018) tool. In this investigation, the T-test was used to evaluate the

mean values for the presence of significant (P≤0.01) differences, while the least significant difference (LSD) was employed to compare means.

Results

Table 1 Summarized the findings of the current study, and it revealed that there was a non-significant difference in ages between patients with breast cancer, newly diagnosed (51.11 ± 2.34) years), and chemotherapy-treated (49.74 ± 2.29 years), as compared with control. (47.70 ± 2.08). The mean ± SE of RBC, Hb, WBC, neutrophil, monocyte, lymphocytes, and PLT**,** showed a highly significant (P≤0.01) decrease in newly diagnosed breast cancer women, with values of (4.15 ± 0.07 10^6 µL, 11.35 ± 0,13 g/dL, 4.65 ± 0.18 10^3 µL, 21.92±2.40%,2.74 ± 0.19%, 19.39 ± 2.46, 231.64 ± 8.30 µL) respectively, and chemotherapy treated breast cancer, (3.21 ±0.0810^6 µL, 8.85 ±0.25 g/dL, 3.27 ± 0.1910^3 µL, 8.53 ± 1.50%, 2.46 ± 0.28%, 8.08 ± 0.96%, 173.19 ± 7.22 10^3 µL) respectively as compared with control (4.50 ± 0.12 10^6 µL, 13.24 ± 0.26 g/dL, 8.06 ± 0.38 10^3µL, 58.19 ± 1.62%, 6.53 ± 0.37%, 30.56 ± 0.97%, and 278.80 ± 13.3210^3 µL) respectively, as shown in Table 1.

Table 1: Age and CBC in breast cancer (newly diagnosed and chemotherapy-treated) and control.

Group	Mean ±SE							
	Age (year)	**RBC (10^6/µL)**	**Hb (g/d)**	**WBC (10^3/L)**	**Neutro (%)**	**Mono. (%)**	**Lymph (%)**	**PLT (10^3/µ)**
Breast cancer (Newly diagnosed)	51.11 ±2.34	4.15 ±0.07 b	11.35 ±0.13b	4.65 ±0.18b	21.92 ±2.40 b	2.74 ±0.19 b	19.39 ±1.04 b	231.64 ±8.30 b
Breast cancer (chemotherapy-treated)	49.74 ±2.29	3.21 ±0.08 c	8.85 ±0.25 c	3.27 ±0.19 c	8.53 ±1.50 c	2.46 ±0.28 b	8.08 ±0.96 c	173.19 ±7.22 c
Control	47.70 ±2.08	4.50 ±0.12 a	13.24 ±0.26a	8.06 ±0.38 a	58.19 ±1.62 a	6.53 ±0.37 a	30.56 ±0.97 a	278.80 ±13.32 a
L.S.D.	6.83 NS	0.260 **	0.635 **	0.681 **	5.86 **	0.805 **	2.98 **	26.20 **
P-value	0.639	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

Means having the different letters in the same column differed significantly.
**** (P≤0.01).**

Table 2 showed there was a highly significant (P≤0.01) increase in IL-8 level in newly diagnosed breast cancer (230.28 ± 1048ng/l) as compared with chemotherapy-treated breast cancer (156.83 ± 9.30 ng/l) and control (194.39 ± 11.36 ng/l). Also, there was a significant decrease in chemotherapy-treated patients compared to control. The mean of TAC level showed a highly significant (P≤0.01) decrease in breast cancer newly diagnosis (2.10 ± 0.12 µmol/l) and chemotherapy-treated (1.51 ± 0.05 µmol/l) as compared with control (7.05 ± 1.02 µmol/l). While there was a non-significant (P≤0.05). Differences between newly diagnosed and chemotherapy-treated breast cancer women.

CRP level in the results revealed there was a highly significant (P≤0.01) increase in breast cancer chemotherapy treated (46.54 ± 1.68 mg/L) as compared with newly diagnosed (37.03 ± 1.16 mg/L) and control (2.29 ± 0.18 mg/L). Also, there was a highly significant (P≤0.01) increase in newly diagnosed as compared with control. VEGF level showed there was a highly significant (P≤0.01) increase in newly diagnosed breast cancer women (2718.95 ± 110.36 ng/l) as compared with chemotherapy-treated (2219.70 ± 37.32 ng/l) and control

(1791.83 ± 108.08 ng/l). Also, there is a highly significant (P≤0.01) increase in the chemotherapy-treated group as compared with the control group, as shown in Table 2.

Table 2: Interleukin – 8, TAC, CRP, and VEGF levels in breast cancer patients (newly diagnosed and chemotherapy-treated) and control.

Group	Mean ±SE			
	IL-8 (ng/L)	TAC (µmol/l)	CRP (mg/L)	VEGF (ng/L)
Breast cancer (Newly diagnosed)	230.28 ±10.48 a	2.10 ±0.12 b	37.03 ±1.16 b	2718.95 ±110.96 a
Breast cancer (chemotherapy-treated)	156.83 ±9.30 c	1.51 ±0.05 b	46.54 ±1.68 a	2219.70 ±87.32 b
Control	194.39 ±11.36 b	7.05 ±1.02 a	2.29 ±0.18 c	1791.83 ±108.08 c
L.S.D.	30.291 **	1.163 **	4.031 **	302.26 **
P-value	0.0001	0.0001	0.0001	0.0001

Means having the different letters in the same column differed significantly.
**** (P≤0.01).**

The results of effect the number of chemotherapy doses showed a highly significant (P≤0.01) decrease in breast cancer chemotherapy treated, in doses (9-20) in RBC, Hb, WBC, Neutrophil, Monocytes, lymphocytes and PLT (3.21 ± 0.18 µL, 8.51 ± 0.49 g/dL, 3.16 ± 0.46, 4.88 ± 0.0069 µL, 1.45 ± 0.28%, 96.48 ± 2.01% and 170.26 ± 19.43 µL) respectively when compared with doses 2-4 (3.73 ± 0.11 10^6µL, 9.25 ± 0.26 g/dL, 4.76 ± 0.3210^3 µL, 16.21 ± 5.38%, 2.94 ± 0.57%, 9.65 1 ± 1.17%, and 183.15 ± 11.82 µL) respectively. In doses of 5-8, the Hb, Neutrophil, and PLT (18.05 ± 0.37 g/dL, 8.62 ± 0.48% and165.93 ±10.31) showed highly significant (P≤0.01) decrease as compared with doses 2-4. In contrast, there were no statically differences in the RBC, WBC, Monocyte lymphocyte and PLT (3.55 ± 0.16 10^6µL, 4.42 ± 0.31 10^3 µL, 3.12 ± 0.48 %, 8.73 ± 1.30%, and 93 ± 10.31 10^3µL). The RBC, WBC, Monocytes, and lymphocytes showed a significant decrease in doses 9-20 when compared with doses 5-8, While Hb, Neutrophil, and PLT showed non-significant differences, as shown in Table 3.

Table 3: CBC in breast cancer patients treated with different doses of chemotherapy.

Number of Doses	Mean ±SE						
	RBC (10^6/µ)	Hb (g/dL)	WBC (10^3/µ)	Neutro. (%)	Mono. (%)	Lympho (%)	PLT (10^3/µ)
Dose: 2-4	3.73 ±0.11 a	9.95 ±0.26 a	4.76 ±0.32 a	16.21 ±5.38 a	2.94 ±0.57 a	9.65 ±1.17 a	183.15 ±11.82 a
Dose: 5-8	3.55 ±0.16 a	8.05 ±0.37 b	4.42 ±0.31 a	8.62 ±.22 b	3.12 ±0.48 a	8.73 ±1.30 a	165.93 ±10.31 b
Dose: 9-20	3.21 ±0.18 b	8.51 ±0.49 b	3.16 ±0.46 b	4.88 ±0.69 b	1.45 ±0.28 b	6.48 ±2.01 b	170.26 ±19.43 b
L.S.D.	0.227 *	1.116 **	1.056 *	7.19 *	1.37 *	2.07 *	38.53 NS
P-value	0.04	0.0012	0.031	0.0163	0.019	0.042	0.570

Means having the different letters in the same column differed significantly.
**** (P≤0.05), ** (P≤0.01).**

Table (4) showed a highly significant (P≤0.01) decrease in IL-8 Level in doses 9-20 (126.76 ± 23.60 hg/L) as compared with dose 5-8 (166.52 ± 23.60 ng/L) and dose (2-4) (173.25 ± 12.21 ng/L). Also, there was a non-significant (P≤0.05) difference between dose 5-

8 and dose 2-4 in the IL-8 Level. While TAC level showed a significant (P≤0.05) decrease in doses 9-20, (1.204 ± 0.16 µmol/l) as compared with doses 5-8, (1.690 ± 0.04 µmol/l) and doses 2-4 1.756 ± 0.12 µmol/l) respectively. While there was no significant difference between dose (5-8) and dose (2-4) in TAC level. The result of the current study revealed a highly significant (P≤0.01) increase in CRP level in doses 9-20 (56.42 ± 2.35 mg/L) as compared with dose 5-8 (46.51±2.74 mg/L) and doses 2-4, (47.25 ± 3.19 mg/L). While there was no significant difference between doses (5-8) and doses (2-4) in CRP Level. The VEGF level showed non-significant differences between different doses of chemotherapy, as shown in Table 4.

Table 4: Interleukin8 (IL-8, TAC, CRP, and VEGF) in breast cancer patients treated with different doses of chemotherapy.

Number of Doses	Mean ±SE			
	IL-8 (ng/L)	TAC (µmol/l)	CRP (mg/L)	VEGF (ng/L)
Dose: 2-4	173.25 ±12.21 a	1.756 ±0.12 a	47.25 ±3.19 b	2217.74 ±134.4
Dose: 5-8	166.52 ±13.67 a	1.690 ±0.04 a	46.51 ±2.74 b	2251.1 ±148.5
Dose: 9-20	126.76 ±23.60 b	1.204 ±0.16 b	56.42 ±2.35 a	2126.1±173.8
L.S.D.	31.133 *	0.308 *	8.189 *	464.68 NS
P-value	0.045	0.041	0.037	0.872

Means having the different letters in the same column differed significantly, * (P≤0.05), NS: Non-Significant.

Discussion

The research limitations in the current study were that we did not go into the different types of chemotherapy for breast cancer, and the different effects for each type of treatment individually, and we also did not take samples from patients with breast cancer that had spread to other parts of the body, such as the liver, bone, or other parts. In this study, the age showed a non-significant difference between the patient and control. The explanation of this result may be due to the selection of samples. Different studies have reported varied mean of age, women under 40 have a low incidence of breast cancer. In the United States, women under 40 account for about 4% of all breast cancers, in Iraq, breast cancer is considered the most common cancer, it ranks the first among the commonest malignancies among the population, there were 6206 cases in 2018, 6094 females and 112 males, the percentage total constituting around 19.70 % with a rate of 16.3 for every 100000 populations [15].
Diagnosed women over 70 had the greatest rates, which start to rise after age 40.The likelihood that a woman's cells will undergo aberrant alterations increases with age. Many of these alterations can lead to the development of cancer [16].

In the present study, the CBC counts for breast cancer patients were significantly decreased in breast cancer (newly diagnosed and chemotherapy-treated groups) as compared with the control group. These results are in agreement with Sharma, found that the CBC count dramatically dropped during the initial chemotherapy treatment phase. No one discusses the prevalence of anemia and transfusion procedures in the preoperative treatment of early TNBC [17]. A decrease in the number of blood cells has been seen when the level of chemotherapy doses increases in breast cancer because of the influence of chemotherapy on the blood generating cells. Although dose dense chemotherapy is linked to a greater incidence of anemia, it has been demonstrated to enhance clinical outcomes for patients with breast cancer. In line with previous research on individuals with breast cancer, the incidence of

anemia was 47.4%. Additionally, Ali clarifies that decreased blood counts are detected as a chemotherapeutic adverse effect following adjuvant treatment [18].

In the present study, it was observed that hemoglobin levels decreases from the first course of chemotherapy and this is similar to many other studies, Kuter. Found that anemia was caused by chemotherapy in the majority of cases and the chemotherapy treatment may all affect the incidence and severity of anemia, the primary purpose of Erythropoietin (EPO) is a type of protein called growth factor used to treat low RBC cells due to the cancer or it is treatment, which is produced in response to tissue hypoxia or severe anemia, is to regulate the bone marrow's blood manufacturing process[19]. A common issue among cancer patients is thrombocytopenia. Thrombocytopenia restricts the frequency and dosage of chemotherapy in addition to the danger of bleeding. It is crucial to check for additional causes of thrombocytopenia when examining patients with thrombocytopenic malignancy. Bleeding and/or the need to postpone treatment can follow a low platelet count. It's crucial to remember that a low platelet level can have many causes, including chemotherapy [8]. The significant elevation in IL-8 level in the breast cancer patients (newly diagnosed) in comparison with the breast cancer chemotherapy-treated and control group is in agreement with the study of, Ali. Who reported that in newly diagnosed breast cancer patients, serum levels of IL-8 are often elevated [18].

Also the current finding in agreement with the study of Sheikhpour stated that one of the primary biomarkers for breast cancer may be IL-8[20]. Bower *et al.* observed five of the six inflammatory indicators measured, including IL-8 and other parameters, showed statistically significant increases from pre to post-treatment in 192 women with early-stage breast cancer who received chemotherapy additionally, compared to normal breast tissue, IL-8 is over expressed in breast cancer[21]. Despite strong evidence that IL-8 may aid in the development and spread of breast cancer, the regulation of IL-8 in the tumor microenvironment is complicated due to the wide range of cells that can secrete it as well as the numerous variables that can influence the expression of IL-8 by these various cell types [22].

Two opposing functional roles of CXCL8 have been proposed in relation to cancer: it can alter the tumor microenvironment to promote tumor genesis and it can strengthen immune regulatory potentials against carcinogenesis. Because BC cells have been shown to express two CXCL8 receptors (CXCR1 and CXCR2), the latter function is more prevalent in BC than the former. Additionally, it has been noted that patients with the ER-ve, ER+ve, and HER-2-ve phenotypes are more likely to have elevated levels of CXCL8 [23]. Because it affects tumor growth, metastasis, and treatment resistance, IL-8 is plays a key role in the biology of breast cancer. It is a major focus of current research in the treatment of breast cancer because of its dual function as a biomarker and a therapeutic target. It has recently been discovered that tumors often coopt the production of this chemokine, which has many pro-tumoral effects in this malignant setting. According to reports, these include angiogenesis, cancer stem cell survival signaling, and the recruitment of myeloid cells that have the capacity to immunosuppress and produce growth factors locally. It has been demonstrated that the blood concentration of IL-8 correlates with the tumor burden in cancer patients since the molecule is mostly produced by the tumor cells themselves. Consequently, it has been demonstrated that IL-8 serum concentrations are helpful as a pharmacodynamics biomarker to detect early response to immunotherapy [24].

The results of the current study showed that, in comparison to breast cancer that was recently diagnosed and control, the TAC level dropped in breast cancer that was treated with chemotherapy. This is consistent with, Xiao *et al*. who found that TAC levels were noticeably

lower in breast cancer patients than in controls. Recent research has shown that antioxidant chemicals do not always have anti-tumor effects. Certain antioxidants aid in the development and spread of cancer [25]. When combined, antioxidants show a duplicitous attitude toward cancer. Antioxidants have also been shown to have two opposing impacts on cancer.
While some antioxidant types exhibit inducer effects on the development and advancement of cancer, others have beneficial effects on cancer treatment [26]. Also, the up regulation of oxidative stress markers and down regulation of the antioxidant defense system are considered the factors that correlate with the initiation and maintenance of breast cancer progression. High levels of base modifications, which are byproducts of DNA oxidation and appear to be linked to breast cancer, have been found in the DNA of breast cancer patients. One such product is 8-hydroxydeoxyguanosine. Women with breast cancer have been found to have elevated urine 8-OHdG levels, and as the cancer progresses, the value of 8-OHdG increases, indicating that ROS may be crucial in the early stages of carcinogenesis [27].
Several investigations have shown that various forms of solid breast cancer have a lower overall antioxidant capacity. Malondialdehyde estimate has recently been used to study oxidative damage in connection to miR-146a expression, suggesting that these two molecules have a dual role in predicting breast tumor geneses [28].

The CRP level, showed there was a highly significant increase in breast cancer chemotherapy treated, as compared with newly diagnosis, and control. These findings in agreement with, Zhu *et al*. CRP level was noted to increase significantly in patients of breast cancer chemotherapy treated with the progression of chemotherapy doses, According to the study, which was based on a large-scale prospective cohort study, elevated CRP concentrations at baseline were linked to an increased risk of incident cancer events during the follow-up [29]. For site-specific cancer, positive associations were also found for cancers of the head and neck, esophagus, stomach, colorectal, liver, lung, breast, kidney cancer, and non-Hodgkin lymphoma, while negative associations were found for CLL.

This could be a sign of the occurrence of infections or treatment-related complications shown that chronic inflammation is associated with an increased risk of cancer. Moreover, a poor prognosis is associated with elevated levels of certain inflammatory markers, such as cytokines, C-reactive protein, and NLR, which are commonly found in cancer patients. One study examining inflammation levels after cancer treatment reported that C-reactive protein and cytokine levels were elevated up to five years after cancer therapy [30]. Carcinogenesis, tumor development, and cancer dissemination all depend on inflammation. The VEGF factor showed an increase significantly in breast cancer newly diagnosed, as compared with chemotherapy-treated and control. These concur with Malekan and Ebrahimzadeh, they noted that proteins potential value as diagnostic biomarkers has already been shown. VEGF proteins may be used as early breast cancer biomarkers, therapy success indicators, and patient survival indicators [13]. Furthermore, anti-cancer treatments may go in the direction of blocking antigenic signaling pathways in the future. Patients with breast cancer may have a higher chance of survival if chemotherapy is paired with anti-antigenic components, nanotechnology, immunotherapeutic medications, and targeted predicates.

The results of treatment with different doses in the present study and revealed a significant decrease in all blood parameters with increase doses of chemotherapy. This could be because of how chemotherapy affects the cells that make blood. These findings are consistent with, Sharma *et al*., they discuss transfusion procedures and the frequency of anemia in the preoperative management of early Triple-negative breast cancer (TNBC) [17]. Although dose-dense chemotherapy is linked to a higher incidence of anemia, it has been demonstrated

to improve clinical outcomes for patients with breast cancer. In line with previous research on individuals with breast cancer, the incidence of anemia was 47.4%.

The results of IL-8 after increasing the doses of chemotherapy in the current study revealed a significant decrease in IL-8 level after receiving 9-20 doses, and which agree with**,** Jiang, they showed**,** chemotherapy resistance is a significant challenge in breast cancer treatment, and have shown that IL-8 expression is significantly activated in response to chemotherapy, contributing to increased drug resistance [31].

This suggests that IL-8 not only plays a role in cancer progression but also in the development of resistance to chemotherapy. Also in chemotherapy-treated patients, increased IL-8 levels can indicate a more aggressive disease and a higher likelihood of treatment resistance. On the other hand, the level of TAC decreased significantly in breast cancer chemotherapy treated dose (9-20).These results are in agreement with Han, antioxidants decrease the risk of breast cancer by reducing oxidative stress, so that the total TAC was significantly lower in patients with long-term treatment with high doses of chemotherapy and this may be the over generation of ROS. Dietary total antioxidant capacity (DTAC) as positively correlated with disease-free survival (DFS), indicating that a diet rich in antioxidants may help reduce the breast cancer recurrence [32]. The results of the current investigation, in which the great majority of patients had extremely low levels of antioxidant capacity, have demonstrated the possible role of decreased blood levels of total antioxidant capacity in breast cancer pathogenicity [28].
CRP showed high levels in patients receiving doses of (9-20) in chemotherapy treated. These deals with, Allin *et al*. they showed; CRP levels reflect the aggressiveness of the tumor and the extent of inflammation within the tumor microenvironment Elevated CRP levels are associated with larger tumor size, the presence of distant metastases, and lower tumor grade. These associations suggest that CRP can serve as a marker for tumor burden and metastatic potential [33].

Conclusion

Cytokines play a major role in the development of breast cancer disease, and the treatment with chemotherapy affects all physiological markers because of the increasing inflammatory condition.

Ethical Clearance

The Research Ethical Committee at scientific research by ethical approval of environmental, health, higher education, and scientific research ministries in Iraq. Under the reference number (No. CSEC/0924/0061).

Conflict of interest

The authors declare that they have no conflict of interest.

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