Interleukin 8 & C-reactive protein-high sensitive levels as predictive markers to hormo-response in breast cancer subtypes BCSs in Syrian patients

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□ ABSTRACT □

Breast cancer is a complex disease with different behaviors and responses to hormone therapy. Inflammatory markers like IL-8 and CRP-hs are often elevated in breast cancer patients. This study aimed to characterize breast cancer subtypes and assess IL-8 and CRP-hs levels in patients at Tishreen-University Hospital in Syria from 2020 to 2022.The study included patients who had mastectomy with lymph node dissection, with an average age of 48.04±10.99 years. Results showed that the most common breast cancer subtypes were Luminal A1, TN, and TP. Older patients and those with Luminal B2 subtype had higher IL-8 and CRP-hs levels, but these differences were not statistically significant. There was a significant relationship between breast cancer subtypes and disease stage .In conclusion, The higher rate of negative ER-expression in Luminal B2 suggests a greater risk for hormone therapy resistance. Additionally, older patients with Luminal B2 subtype had higher IL-8 and CRP-hs levels. These findings enhance our understanding of breast cancer subtypes, their association with inflammatory markers, and hormone therapy resistance. Further research is needed to validate these results and explore potential therapeutic implications.

Keywords: breast cancer, IL-8, CRP-hs

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الأنترولوكين8 والبروتين التفاعلي C عالي الحساسية كمشعرات تنبؤية لـ لاستجابة الهرمونية لأنواع سرطان الثدي لدى مريضات سرطان الثدي في سوريا

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□ ملخّص □

يعدُّ سرطان الثدي من الأمراض المعقدة التي لها استجابات مختلفة للعلاج الهرموني والتي تترافق غالباً مع ارتفاع علامات الالتهاب مثل الانترولوكين-8 (IL-8) والبروتين التفاعلي عالي الحساسية C (CRP-hs). تهدف هذه الدراسة إلى توصيف الأنواع الفرعية لسرطان الثدي وتقييم مستويات IL-8 و CRP-hs لدى مريضات سرطان الثدي في مستشفى تشرين الجامعي في سوريا من عام 2020 حتى 2022، إذ شملت هذه الدراسة المريضات ممن خضعن لاستئصال الثدي مع تشريح العقد الليمفاوية، بمتوسط عمر 48.04 ± 10.99 سنة. أظهرت النتائج أن الأنواع الفرعية لسرطان الثدي الأكثر شيوعًا هي Luminal A1 والسرطان سلبي المستقبلات الثلاث) أستروجين وبروجسترون و TN (Her-2والسرطان إيجابي المستقبلات الثلاث) أستروجين وبروجسترون و TP. (Her-2
كان لدى المريضات الأكبر سنًا وأولئك الذين يعانون من النوع الفرعي Luminal B2 مستويات أعلى من IL-8 و CRP-hs مقارنةً مع بقية المجموعات، لكن هذه الاختلافات لم تكن ذات دلالة إحصائية لكن كان هناك علاقة مهمة بين الأنواع الفرعية لسرطان الثدي ومرحلة المرض كما يشير المعدل الأعلى لتعبير مستقبل الأستروجين السلبي ER في Luminal B2 إلى وجود خطر أكبر لمقاومة العلاج الهرموني. بالإضافة إلى ذلك، كان لدى المرضى الأكبر سنًا الذين يعانون من النوع الفرعي Luminal B2 مستويات أعلى من IL-8 و CRP-hs . تعزز هذه النتائج فهمنا للأنواع الفرعية لسرطان الثدي، وارتباطها بعلامات الالتهاب، ومقاومة العلاج الهرموني وهناك حاجة إلى مزيد من البحث للتحقق من صحة هذه النتائج واستكشاف الآثار العلاجية المحتملة

الكلمات المفتاحية: سرطان الثدي، الأنترولوكين-8، البروتين التفاعلي C عالي الحساسية

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Introduction

Notable incidence of Breast Cancer (BC) as common cancer among women worldwide is remarked with an estimated 240,000 new cases in the US in 2013.[1] According to the world health organization (WHO) in 2020, 4388 women were diagnosed with BC in Syrian Arab Republic [2,3] Great interest in strategies of therapy and tumoral microenvironment-associated has been the focus of several clinical types of research for early diagnosis, prevention, and prognosis.

Different responses to hormone therapy according to Estrogen receptor expression (ER), Progesterone receptor expression (PR), and human epidermal growth factor receptor 2 - expression (Her-2) status had been confirmed in BC.[4] Breast Cancer Subtypes (BCSs) according to hormone receptors status could also vary according to tumor and patients characteristics such as age, stage, histological grade, and involved lymph nodes.

Recently, various studies had been investigated molecular BCSs with different expression statuses of ER, PR receptors, and Her-2 receptors and different staining intensity degrees, especially low expression of ER.[5] In fact, these subtypes vary in patients remarkably. Therefore; overall survival (OS) and response to radio/chemotherapy were also different.[6,7]

Additionally, Her-2 overexpression with ER-negative is present in approximately 20-30% of all human breast cancer, while Triple- Negative breast cancer TN is present in approximately 15-20% of all diagnosed cases.[8,9]

Therefore, the development of an effective protocol of treatment for these heterogenic forms of BCSs presents a challenge in selecting suitable protocols for chemo/hormonal therapy with maximum safe preventive and minimum toxic effects.

Malignant changes begin with an inflammation state in the microenvironment of a tumor. Various studies had been reported an association between inflammatory mediators such as serum levels of C Reactive Protein (CRP), CRP high sensitivity (CRP-hs), interleukin-6 (IL-6), and Interleukin-8 (IL-8), and elevated risk of various types of cancer.[10] Strong association of inflammatory mediators is remarked with lung cancer, weak association with breast, prostate, and colorectal cancers which support the role of chronic inflammation low-grade in carcinogenesis.[11] CRP is synthesized in hepatocytes in response to cytokines and released from leucocytes within the tumor microenvironment. CRP is raised in circulation in response to acute inflammation, infection, and tissue damage, and its elevated levels are proportional to the degree of tissue damage. Higher serum levels of CRP are investigated in invasive cancer than in non-invasive cancer.[11]

Interleukin-8 (alternatively known as CXCL8) is a pro-inflammatory cytokine involved in the inflammation response, complex effects on the tumor microenvironment may result in tumor proliferation, survival, and chemo-resistance in malignant disease. IL-8 is produced by a wide variety of cell types, including monocytes, neutrophils, fibroblasts, and endothelial cells. It serves as a chemical signal that attracts neutrophils at the site of inflammation known as the "neutrophil chemotactic factor". However, recent studies indicate that IL-8 can promote Cancer Stem Cell (CSC) invasion, metastases, poor prognosis, and treatment resistance.[12]

Breast cancer is the first solid tumor in which CSCs were identified. High IL-8 serum levels and tumor expression are known to be associated with poor patient prognosis in many malignant diseases, including breast cancer. Even in localized breast cancer, patients with high circulating IL-8 levels have a poorer prognosis than patients with low IL-8 levels.

Serum IL-8 level is increased in breast cancer but the mechanism by which IL-8 contributes to breast cancer progression is still unknown. Targeting CXCR1/2 signaling has proven efficacious in vivo models of primary invasive and metastatic breast cancers, catalyzing the initiation of clinical trials evaluating CXCR1/2 inhibitors.[12]

Breast cancer is a heterogeneous disease on the morphologic, immunohistologic, and molecular levels, different phenotypes present varying clinical behaviors.

The aims of this prospective study were the classification of breast cancer subtypes (BCSs) depending on ER, PR, and HER-2 expression status, and the characterization of these BCSs according to plasma IL-8, CRP-hs levels, and other tumor characteristics.

Methodology

Population of Study: 48 Patients diagnosed with breast cancer were enrolled in current study. Patient's charts were reviewed, with respect to pathology report, operative report, and clinical outcomes. A written consent was signed by every patient and approved by the Institutional Ethical Board.

Patients had been admitted to Tishreen University Hospital (TUH) – Lattakia - Syrian Arab Republic between December 2020 and December 2022. Basic blood investigations and chest X-rays were done for all the patients. Patients aged between 25 and 74 years old. Patients with acute- inflammation state cardiovascular diseases and with Type-2 diabetes had been excluded.

-Clinical history

Patients underwent a total or a subtotal (left or right) mastectomy with axillary lymph node dissection, and the number of lymph nodes excised was different in patients.

Data based on pathology reports included tumor size (cm), stage, histologic grade, and number of lymph -nodes excised (positive and total number) were obtained prospectively.

Patients were diagnosed as Invasive Ductal Carcinoma (IDC), Invasive Lobular Carcinoma (ILC), and Mucinous carcinoma (MC).

Breast cancer staging system:According to the pathological TNM Staging according to the American Joint Committee on Cancer (AJCC), patients were assessed as following:

T; Tumor size: (T1 ≤2 cm, T2: 2.1-5 cm, T3 >5 cm, T4 = chest wall or skin infiltration)

N; Nodal staging: (pN1: 1-3 nodes, pN2: 4-9 nodes, pN3: ≥ 10 nodes, NX: Nearby lymph nodes cannot be assessed, and N0: Cancer has not spread to nearby lymph nodes).

-Breast Cancer Subtypes (BCSs) classification according to ER, PR, and Her- expression status:

Breast Cancer Subtypes (BCSs) were classified in patients according to ER, PR, and Her-2/ neu receptors expression status as follows into five subtypes:

- Triple Positive TP = luminal B1 (ER+, PR+, and Her-2+).
- Triple Negative TN (ER-, PR-, and Her-2-).
- Luminal A1 (Her-2 -, ER+, and PR+).
- Luminal A2 (Her-2 -, ER+, and PR-).
- Luminal B2 (ER+, PR-, and Her-2+).
- Her-2+ (ER-, PR-)

-Assays for plasma IL-8 and CRPhs levels: The samples were collected after surgical procedures

Plasma CRP-hs levels were measured by LATEX-high sensibility determination using a BioSystem kit (Spain), The agglutination of the latex particles is proportional to the CRP concentration and can be measured by turbidimetry. Reference ranges were depending on age as follows:

- <3.33mg/l for 19-49 years
- <8.50mg/l for 50-64 years
- <6.60mg/l for 65-99 years

IL-8 levels were measured in plasma samples collected on sterile EDTA by Enzyme Amplified Sensitivity Immuno-Assay (EASIA) using DIA source IL-8-EASIA Kit (Belgium) and the reference range was <130 pg/ml.

Statistical Analysis:

Descriptive statistics using frequencies (%) for categorical data were calculated. The chi-square test was used to compare percentages between groups. Two-sample Wilcoxon rank-sum (Mann-Whitney) test and Kruskal-Wallis test were used for comparing means of serum CRP levels. All analyses were completed using the Statistical Package for the Social Sciences (SPSS) version 18 (IBM Corporation). As the analysis involves multiple subgroups, significance was set at the 5% level (P.value < 0.05).

Results And Discussion

Characteristics of patients and tumor status

37 patients (77.08%) out of 48 breast cancer patients were diagnosed with IDC which was the most common histologic type, while 11 were diagnosed with ILC (22.92%). Female patients were distributed by age into two groups: group (1): patients aged younger than 46 years (n=22, 45.83 %), and group (2): patients of 46 years and older (n=26, 54.17%) with a mean of 48.04±10.99. Patients were distributed into four groups according to tumor size: T1 (n=2, 4.17%), T2 (n=28, 58.33%), T3 (n=14, 29.16%), and T4 (n=4, 8.33%). Patients were divided according to Histologic Grade as follows: Grade I: 2 patients (4.17%), Grade II: 26 patients (54.17%), Grade III: 20 patients (41.67%). Stage- distribution was as follows: stage IIA and IIB: 18 patients (37.50%), stage IIIA and IIIB: 26 patients (54.17%), and 4 patients were staged as stage IV (8.33%). Concerning pN staging; 3 patients (6.25%) were with NX, 9 patients (18.75%) were with N0, 10 patients (20.83%) were with N1, 6 patients (12.5%) were with N2 and 20 patients (41.66%) were with N3. All characteristics of patients and tumor status are summarized in **Table 1**.

Table 1: Characteristics of patients and tumor status

		n	%
Age, years	<46	22	45.83
	≥46	26	54.17
Tumor Size, cm	T1: ≤2	2	4.17
	T2: 2.1 to 5	28	58.33
	T3: >5	14	29.16
	T4	4	8.33
Diagnosis	IDC	37	77.08
	ILC	11	22.92
Histologic Grade	I	2	4.17
	II	26	54.17
	III	20	41.67
Histological Stage	IIA	10	20.83
	IIB	8	16.67
	IIIA	6	12.5
	IIIB	20	41.67
	IV	4	8.33

Nodal stage, pN	NX	3	6.25
	N0	9	18.75
	N1	10	20.83
	N2	6	12.5
	N3	20	41.66

Breast Cancer subtypes according to ER-receptor, PR-receptors and Her-2/neu receptor expression status

Concerning hormone receptors (ER, PR) and Her-2 expression, our results found that 25 patients were ER-receptor positive (52.08%), 18 patients were PR-receptor positive (37.5%), 16 patients were positive for Her-2 receptor and PR-receptor (33.33%), and 15 patients were Her-2 receptor positive (31.25%) as shown in **Table 2**; the most number of patients were negative for Her-2, positive for ER and PR.

Table 2: Hormones Receptors status and BCSs

		n	%
ER status	Negative	23	47.92
	Positive	25	52.08
PR status	Negative	30	62.5
	Positive	18	37.5
Her-2 status	Negative	33	68.65
	Positive	15	31.25
Triple Positive TP = luminal B1 (ER+, PR+, and Her-2+)		2	4.1
Triple Negative TN (ER-, PR-, and Her-2-)		12	25
Luminal A1 (Her-2 -, ER+, and PR+)		16	33.33
Luminal A2 (Her-2 -, ER+, and PR-)		5	10.41
Luminal B2 (ER+, PR-, and Her-2+)		2	4.1
Her-2+ (ER-, PR-)		11	22.9

Distribution of Breast Cancer subtypes according to plasmaIL-8, CRP-hs levels and age

Table 3 shows the distribution of BCSs according to plasmaIL-8 and CRP-hs levels. Results confirmed that plasma IL-8 level was high in Luminal B2 group, and TN group while the lowest level was in TP subtype, but the difference was not significant. Mean of IL-8 levels was 137.65 ± 257.91.

Concerning CRP-hs levels; the difference was statistically significant between subtypes (p.value=0.008) as shown in **Table 3**. Mean of CRP-hs levels was 10.37± 8.38 mg/l. Table 3 showed that patients with mean of age of 67± 9.89 years were Luminal B2 in comparison with TP patients with age of 46±5.65 years, but the differences were not significant.

Table 3: Distribution of Breast Cancer subtypes according to IL-8 and CR-Phs levels

	TP N=2	TN N=12	Luminal A1 N=16	Luminal A2 N=5	HER-2+(ER-, PR-) N=11	Luminal B2 N=2	P-value
Age (Years)	46 ± 5.65	47 ± 12.52	47 ± 10.38	47.80 ± 9.20	47.50 ± 11.09	67 ± 9.89	0.296
Plasma IL-8 (pg/ml)	Mean ±SD: 137.65± 257.91 pg/ml -Range: (21.63 - 1535.2)						
	39.45 ± 8.01	200.04 ± 4.21	140.17 ± 177.7	50.62 ± 25.31	59.11 ± 41.57	482.45 ± 22.56	0.318
Mean ±SD: 10.37± 8.38 mg/l - Range: (5.12 - 18)							
hc-CRP (mg/l)	11.48 ± 0.57	12.06* ± 2.46	9.07°* ± 2.8	9.07¤* ± 2.2	11.90° ± 3.41	15.55°¤ ± 0.72	0.008*

Classification of Breast Cancer subtypes according to tumor characteristics

As shown in **Table 4**, patients classified in BCSs were reclassified according to tumor characteristics. Results confirmed that the relation between BCSs and stage was statistically significant (p.value=0.03). Most number of patients was with Luminal A1 with stage II or III as shown in figure 1. There was no significant relation with grade, tumor size or nodal stage.

Table 4:Classification of Breast Cancer subtypes according to tumor characteristics

		TP N=2	**TN N=12**	**Luminal A1 N=16**	**Luminal A2 N=5**	**HER-2+(ER-, PR-) N=11**	**Luminal B2 N=2**	**P-value**
Diagnosis		ILC: 2	IDC: 8 ILC: 4	IDC:14 ILC: 2	IDC: 4 ILC: 1	IDC:10 ILC:1	IDC: 1 ILC: 1	0.07
GRADE	**I**	-	-	1	-	1	1	0.223
	II	-	4	11	4	4	-	
	III	2	7	4	1	5	1	
	missing	-	1	-	-	1	-	
STAGE	IIA	-	3	5	1	1	-	**0.03***
	IIB	-	1	4	-	2	1	
	IIIA	-	2	1	2	1	-	
	IIIB	-	5	6	2	6	1	
	IV	2	1	-	-	1	-	
Tumor	T1	-	-	1	-	1	-	0.644

size (cm)	T2	-	6	12	3	6	1	
	T3	1	4	3	2	3	1	
	T4	1	2	-	-	1	-	
N staging	N0	-	3	4	1	1	-	0.63
	N1	-	2	5	-	2	1	
	N2	-	1	1	2	2	-	
	N3	1	5	6	2	5	1	
	Nx	1	1	-	-	1	-	

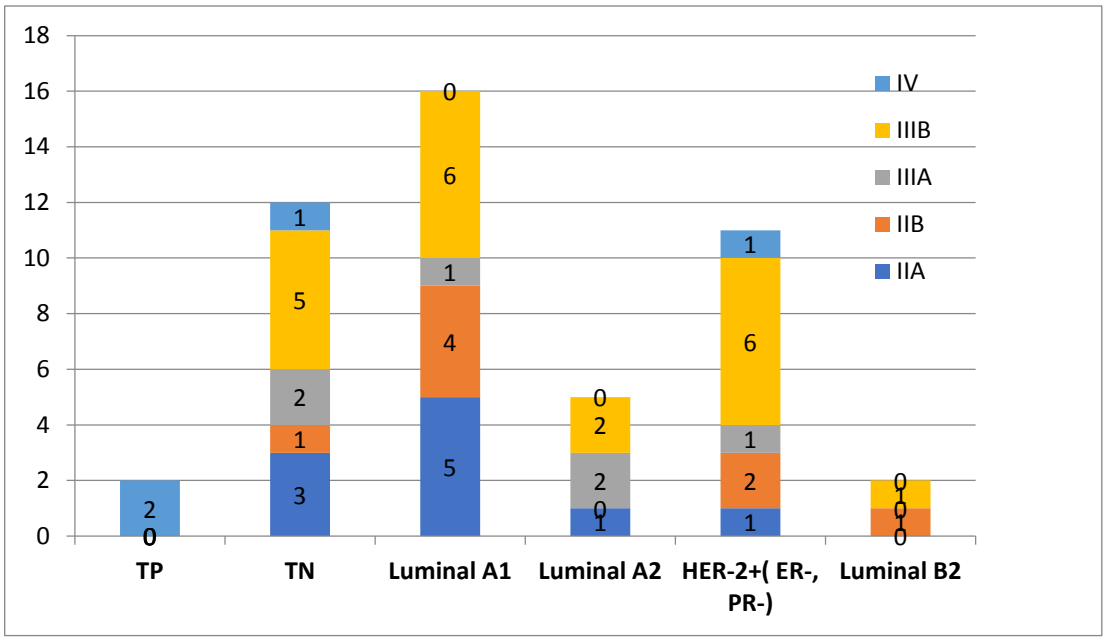

Figure1: Classification of BCSs according to histological Stage

Characteristics of patients and tumor associated with IL-8 levels

Most number of patients was diagnosed as IDC as common diagnosis, and in negative Her-2 expression. In Syrian Arab Republic , the incidence of breast cancer increases relatively with enormous costs and notable mortality rates. Resistance to endocrine therapy or chemotherapy is remarked in many cases. Concerning hormone receptor expression status, accumulated results confirmed high variation in breast cancer subtypes (BCSs) regarding homogeneity in histological diagnosis, stage, and grade.

Recent research had been investigated a novel approach: the elimination of Breast Cancer Stem Cells (BCSC) by using Repertaxin which is a combination of CXCR1/CXCR2 inhibitors with Her-2 target therapy [13]. These findings propose the inflammation hypothesis, and the role of inflammation mediators such as CRP, CRP-hs, IL-8, and IL-6 as plasma markers in addition to classical tumor markers [14]. Therefore, a great need to evaluate the inflammation state and to identify patients according to BCSs who might benefit most from specific treatments with less toxic-effect.

The current study was conducted on 48 breast cancer patients aged from 25 to 74 years old in Tishreen University Hospital- Lattakia –Syria during 2020- 2022. The main goals of our study were to classify patients according to ER, PR, and Her-2expression status into BCSs, and to

evaluate the relationship of these BCSs with inflammation state (plasma IL-8 and CRP-hs levels) and other tumor and patient characteristics.

Concerning general characteristics of patients and tumors, results showed that 37 patients (77.08%) were diagnosed with IDC as a common diagnosis of breast cancer. 28 patients (58.33%) were with T2 as the common size of the tumor (cm).

Rate of BC subtypes according to hormones expression status: Most patients (n=16, 33.33%) were diagnosed as Luminal A1 (Her-2 -/ER+/PR+), 12 patients were TN (25%) as a risk group for hormone-therapy resistance regarding the elevated number of patients with Her-2– and PR- remarked in our study. Other studies remarked a similar ratio of triple-negative breast cancer with approximately 15-20% of tumors diagnosed [15]. Shahla B et al, in 2022 confirmed that both TNBC and weak ER+ tumors (staining <10%) were more commonly observed among patients <60 years of age compared with older patients [16]. Our results also showed that the mean age of patients was 48.04±10.99 years old with a range from 25 to 74 years old, and that supports the results by Shahla B et al. Patients with Luminal B2 (Her-2+, ER-/PR+) were with a mean age of 67±9.89 years in comparison with younger patients. TP was the lowest subtype noted in the current study with only 2 patients (4.17%) who were TP, and this proposes additional challenges for hormone therapy. According to IL-8 levels, results confirmed that most patients were with plasma IL-8 levels <130 pg/ml, and the differences with tumor characteristics were no significant

Table5: Characteristics of patients and tumor associated with IL-8

Parameter		plasma IL-8 levels (pg/ml)				P value
		<130 pg/ml		≥130pg/ml		
		n	%	n	%	
Age, year	<46	19	86.36	3	13.64	0.221
	≥46	19	73.08	7	26.92	
Tumor Size, cm	≤2cm	1	50	1	50	0.278
	2.1 to 5	22	75.86	7	24.14	
	>5	15	88.24	2	11.76	
Diagnosis	IDC	29	78.38	8	21.62	0.587
	ILC	9	81.82	2	18.18	
Histologic Grade	I	2	100	0	0	0.674
	II	19	73.08	7	26.92	
	III	17	85	3	15	
Stage	IIA	8	80	2	20	0.283
	IIB	4	50	4	50	
	IIIA	5	83.33	1	16.67	
	IIIB	17	85	3	15	
	IV	4	100	0	0	
Nodal stage, pN (N)	0	7	87.5	1	12.5	0.705
	1 to 3	19	79.17	5	20.83	
	>3	9	69.23	4	30.77	
ER status	Neg	19	82.61	4	17.39	0.419
	Pos	19	76	6	24	
PR status	Neg	25	83.33	5	16.67	0.287
	Pos	13	72.22	5	27.78	
Her-2 status	Neg	24	75	8	25	0.271
	Pos	14	87.5	2	12.5	

Results confirmed that the relation between BCSs and stage was statistically significant (p.value=0.03); most patients with Luminal A1 were with stage II or III.

Plasma IL-8 and CRP-hs levels: The inflammation state as a part of the microenvironment of the tumor was estimated by measuring plasma IL-8 and CRP-hs levels for all patients. Results confirmed that the elevated levels of IL-8 were remarked in Luminal B2 (ER+, PR-, and Her-2+) with a mean of (482.22±22.56 pg/ml). Other studies support the hypothesis of inflammation state and that IL-8 can promote Cancer Stem Cell (CSC) invasion, poor prognosis, and treatment resistance in Luminal B2 or in ER- as high-risk BCSs [12]. These results need more investigation concerning follow-up of patients to evaluate metastasis and prognosis. The mean of IL-8 levels was not significant with characteristics of tumor such as tumor size, grade, stage, and lymph nodes as shown in results, and this may be explained by moderate levels of IL-8 in all patients with mean<130 pg/ml in most patients, noted that most tumors were T2, GII, and Stage II, III.

Our results showed also that Luminal B2 patients were with elevated levels of CRP-hs in comparison with Luminal A1 patients with significant differences between subtypes (p.value= 0.008). These results support the efficacy of plasma CRP-hs levels for expecting resistance to anti-ER therapy as a poor prognosis subtype.

Moderate levels of CRP-hs and IL-8 remarked in all patients could be explained by considering the procedures of serum measurement. In fact, inflammation mediators were measured after surgery-mastectomy of the breast in all patients and before any treatment, regarding that most patients were with stage II and III as early histological states; which eliminate the activity of CSC in advanced cases, but this is still unclear and need more investigations. Measuring is also performed after excluding acute inflammation states, and this may propose a chronic-grade inflammation. It had been reported by Al-Shimaa Mahmoud Abas in 2022 that additional diagnostic biomarkers could be added to classical characteristics of invasive tumors [17].

Sanmamed MF et al in 2017 confirmed that rising IL-8 levels during treatment could be a sign of chemo-resistance, and it, therefore, might be beneficial to refer patients with rising IL-8 levels to new treatment modalities [18].

BC subtypes should be confirmed to evaluate the pathologic complete response (pCR) rate after neoadjuvant chemotherapy [19]. There were a limited number of patients and missing data preventing us from studying important variables, such as follow-up of patients to assess the recurrence-free survival or overall survival and to evaluate the protocol of therapy in our analyses.

Statement of Ethics: .

Written informed consent was obtained from all participants. This study was performed according to the guidelines of Tishreen University, which abides by the Helsinki Declaration on ethical principles for medical research involving human subjects

Conflict of interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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