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Pre treatment Neutrophil to Lymphocyte Ratio and Total Cholesterol Levels as Biomarkers for Breast Cancer

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ABSTRACT

Background: Breast cancer is one of the most common cancers worldwide. The effectiveness of treatment in different breast cancer types depends on clinicopathological characteristics. Several factors can influence tumor aggressiveness, with the neutrophil-to-lymphocyte ratio (NLR) and total cholesterol (TC) being among the most prevalent. Due to the limited number of studies evaluating the relationship between these markers and tumor stage, this study aimed to investigate the role of NLR and total cholesterol as biomarkers in relation to breast cancer stage.

Methods: We evaluated 101 newly diagnosed breast cancer patients and analyzed NLR and total cholesterol (TC) in relation to clinicopathological parameters, based on cut-off values determined using the Receiver Operating Characteristic (ROC) curve.

Results: Breast cancer stage was significantly associated with NLR, total cholesterol, neutrophil count, and white blood cell (WBC) count ($p < 0.05$). Based on tumor stage, cut-off values were determined to be 2 for NLR and 194 mg/dL for total cholesterol, considering the optimal points of sensitivity and specificity from the ROC curve. Higher NLR was significantly associated with increased tumor size ($p = 0.004$) and lymph node metastasis ($p = 0.021$). Higher total cholesterol was associated with increased BMI ($p = 0.002$), tumor size ($p = 0.04$), lymph node metastasis ($p = 0.001$), and tumor grade ($p = 0.013$). Additionally, higher NLR was significantly associated with increased total cholesterol levels ($p = 0.004$).

Conclusions: Pretreatment NLR and total cholesterol may serve as useful predictors of breast cancer stage. Elevated levels of NLR and total cholesterol were associated with more advanced tumor characteristics. Further large-scale studies are recommended to explore their association with survival and recurrence rates.

Keywords: Breast cancer, NLR, total cholesterol.

INTRODUCTION

Breast cancer is considered one of the most common cancers among women around the world [1],[2]. It is estimated that about 2.3 million cases were diagnosed worldwide in 2020, especially in industrial countries, with an increasing number of new cases diagnosed globally [3],[4]. It occurs and develops due to various factors including genetic and environmental factors. Many associated risk factors such as hormonal, physiological, and nutritional factors are related to lifestyle [4]. Clinical outcomes in breast cancer differ significantly from one patient to another depending on several variables and clinicopathological factors [5],[6]. According to different studies, the impairment in inflammatory response plays a crucial role in tumor development. For this purpose, many markers can reflect the systemic inflammatory response. One of these markers is neutrophils to lymphocytes ratio

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(NLR) [7]. Recent studies evaluated the NLR correlation with clinical characteristics among breast cancer patients such as(stage, grade, tumor size, and metastasis…) and they reported equivocal results with many findings showing no correlation, while others indicated a positive relationship [8],[9]. several tumor- derived molecules affect inflammatory cells in the tumor microenvironment; Cholesterol and its metabolites are common examples [10]. Many studies reported that serum total cholesterol was a risk factor for breast cancer. These studies demonstrated that its metabolite 27Hydroxy cholesterol (27HC) is important in tumor progression and metastasis [11],[12]. The relationship between NLR and total cholesterol levels among breast cancer patients was assessed by Dominguez *et al.* ; they found a significant statistical correlation between NLR values and total cholesterol levels.[13]

NLR and total cholesterol (TC) are inexpensive, affordable, and widely applicable in clinical practice. However, due to the shortage of studies evaluating the association between the previous markers and breast cancer stage in Syria, we aimed in this study to assess the pretreatment NLR and total cholesterol. We also evaluated their relationship with some clinicopathological parameters such as (grade, tumor size, lymph node metastasis, distant metastasis, hormonal receptors, histological and molecular subtypes) in a group of breast cancer patients using optimal cutoff values determined depending on tumor stage. This can help us predict breast cancer progression.

Materials And Methods

This study was conducted at Tishreen University Hospital (TUH) in Lattakia City, Syria from December 2022 to January 2024. It was confirmed by the institution's ethics board of Tishreen University and formal acceptance was obtained from all participants.

Study design and exclusion criteria:

This study evaluated 101 newly diagnosed breast cancer patients before receiving any treatment, who were admitted to the chemotherapy and radiotherapy center at TUH. All patients' complete demographical, medical, and pathological data were ensured before including them in the study sample. Clinical stages were classified into early stage (1-2) and advanced stage (3-4) [14].

We excluded patients with infections or inflammatory diseases, autoimmune diseases, steroid administration, and statin therapy.

Analytical methods:

Venous blood samples were assembled from each participant. A Complete blood count (CBC) was performed using an auto hematology analyzer to obtain the absolute count of white blood cells, neutrophils and lymphocytes. NLR ratio was determined by dividing the absolute neutrophil count by the absolute lymphocyte count. While total cholesterol was measured using the enzymatic method by Mindray BS-380 analyzer (China), serum total cholesterol less than 200mg/dl was considered normal.

Statistical analysis:

The study was tested using the statistical package for social science (SPSS V22). The Kolmogrov Smirnov test (KS-test) determined the normality of distribution. Data were introduced as mean± standard deviation for continuous variables and percentages for categorical variables.

Student *t*-test and Mann Whitney test were used for comparing means between two groups depending on variables' distribution and the Chi-square or Fisher exact test was used for categorical data. Cut-off points for the two variables were determined using the ROC curve (receiver operating characteristic curve) by considering the sensitivity and specificity value. A P-value less than 0.05 was considered statistically significant.

Results:

1- Patient characteristics:

The study included 101 breast cancer patients divided according to tumor stage into early stage 1-2 (48 patients)

and advanced stage 3-4 (53 patients).The patients were staged clinically according to tumor, node, and metastasis (TNM) staging issued by the American Joint Committee on Cancer (AJCC), 8th edition [15].

There were no significant differences in age, menopause, BMI, and tumor grade between the two groups. However, when comparing the hematological parameters and total cholesterol, we found that both groups differ significantly in WBC count (p=0.016), neutrophil count (p=0.003), NLR(p=0.001) and serum total cholesterol (p=0.001) whereas there was no significant difference in lymphocyte count(p>0.05).

Table 1 compares early and advanced-stage groups' demographical, pathological, and hematological parameters.

Table1: Patients characteristics and blood parameters according to tumor stage

characteristic	**Early(n=48)**	**Advanced(n=53)**	**p-value**
Age(years)	49.73±9.55	53.72±12.73	0.076
Menopause(%)			
Premenopause	22(45.8%)	18(34%)	0.22
Postmenopause	26(54.2%)	35(66%)	
BMI(%)			
Normal weight(<25kg/m²)	18(37.5%)	15(28.3%)	
Over-weight(25-29.9 kg/m²)	19(39.6%)	24(45.3%)	
Obesity(≥30kg/m²)	11(22.9%)	14(26.4%)	0.61
Grade(%)			
Grade1	5(10.4%)	4(7.5%)	
Grade2	29(60.4%)	21(39.7%)	0.054
Grade3	14(29.2%)	28(52.8%)	
Blood parameters			
White blood cells(10^6/µl)	7.01±1.97	7.89±2.27	**0.016***
Neutrophils(10^6/µl)	4.35±1.42	5.31±1.86	**0.003***
Lymphocytes(10^6/µl)	2.24±0.77	2.13±0.84	0.21
NLR	1.90±0.59	2.77±1.26	**0.001***
Total cholesterol(mg/dl)	170±31.02	219±47.15	**0.001***

P<0.05*

2- ROC curve, sensitivity, and specificity of NLR and total cholesterol (TC) as predictive markers of breast cancer stage:

ROC analysis was carried out to determine the optimal cutoff points for NLR and total cholesterol. It has been found that AUC (Area Under Curve) was >0.70 which indicated that both NLR and total cholesterol could be used as predictive markers for the advanced stage of breast cancer. NLR had 73.6% sensitivity, and 70.8% specificity with a cut-off value of 2 while total cholesterol had 75.5% sensitivity, and81.2% specificity with a cut-off value of 194 mg/dl. Table 2 performs ROC analysis details.

Table 2: AUC, cut-off values, sensitivity, and specificity of NLR and total cholesterol for predicting the advanced stage of breast cancer:

parameter	**AUC**	**95%Cl**	**Cut-off value**	**Sensitivity%**	**Specifity%**	**p-value**
NLR	0.74	0.643-0.838	2	73.6%	70.8%	0.001*
TC	0.82	0.744-0.906	194	75.5%	81.2%	0.001*

*P<0.05

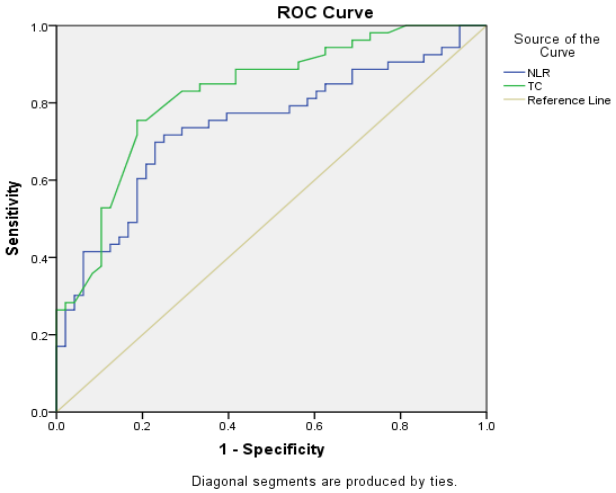

Figure 1: ROC curve of NLR and TC as predictive values of the advanced stage of breast cancer

3- Comparison of clinicopathological characteristics of breast cancer patients according to the high and low NLR:

Among 101 breast cancer ,45 patients had low NLR(NLR<2) , while 56 patients had high NLR(NLR≥2). High NLR values were significantly associated with increased tumor size(p=0.005) and lymph node metastasis (p=0.021). High NLR values were not associated with age, menopause, BMI, distant metastasis, hormonal status, histological and molecular subtypes. Baseline clinicopathological factors and the comparison according to NLR values are summarized in Table3:

Table3: Comparison of clinicopathological factors of breast cancer patients between high NLR and low NLR groups

Variables	Category	N	Low NLR (<2) (N=45)	High NLR (≥2) (N=56)	P-Value
Age (years)	< 40	15	6 (13.3%)	9(16.1%)	0.72
	40-60	63	30(66.7%)	33(58.9%)	
	>60	23	9(20%)	14(25%)	
Menopause	Premenopause	61	27(60%)	34(60.7%)	0.94
	Postmenopause	40	18(40%)	22(39.3%)	
BMI (Kg/m²)	Normal weight (<25)	33	14(13.1%)	19(33.9%)	0.45
	Over-weight (25-29.9)	43	22(48.9%)	21(37.5%)	
	Obesity (≥30)	25	9(20%)	16(28.6%)	
Grade	Grade1	9	5(11.1%)	4(7.1%)	0.15
	Grade2	50	26(57.8%)	24(42.9%)	
	Grade3	42	14(31.1%)	28(50%)	
Tumor size	T1(Tumor size<2cm)	9	5(11.1%)	4(7.1%)	**0.004***
	T2 (2cm<Tumor size≤5cm)	62	34(75.6%)	28(50%)	
	T3 (Tumor size>5cm) + T4 (Tumor of any size growing into chest wall and skin)	30	6(13.3%)	24(42.9%)	

Variables	Category	N	Low NLR (<2) (N=45)	High NLR (≥2) (N=56)	P-Value
Lymph node metastasis	N0(No involved lymph nodes)	43	26(57.8%)	17(30.4%)	**0.021***
	N1(1-3 involved lymph nodes)	23	8(17.8%)	15(26.8%)	
	N2(4-9 involved lymph nodes) +N3(≥10 involved lymph nodes)	35	11(24.4%)	24(42.9%)	
Distant metastasis	M0	97	44(97.8%)	53(94.6%)	
	M1	4	1(2.2%)	3(5.4%)	0.62
ER (Estrogen receptors)	Negative	34	13(28.9%)	21(37.5%)	
	Positive	67	32(71.1%)	35(62.5%)	0.36
PR (Progesteron receptors)	Negative	52	22(48.9%)	30(53.6%)	0.64
	Positive	49	23(51.1%)	26(46.4%)	
HER2(Human epidermal growth factor receptor-2)	Negative	71	31(68.9%)	40(71.4%)	0.78
	Positive	30	14(31.1%)	16(28.6%)	
Histological types	IDC (Invasive Ductal Carcinoma)	87	36(80%)	51(91.1%)	0.27
	ILC (Invasive Lobular Carcinoma)	9	6(13.3%)	3(5.4%)	
	Others	5	3(6.7%)	2(3.6%)	
Molecular subtypes	Luminal A	51	22(48.9%)	29(51.8%)	
	Luminal B	20	10(22.2%)	10(17.9%)	
	HER2-overexpression	10	4(8.9%)	6(10.7%)	0.95
	TNBC (Triple negative breast cancer)	20	9(20%)	11(19.6%)	

*P<0.05

4- Comparison of clinicopathological characteristics of breast cancer patients according to the high and low TC:

Using the total cholesterol cut-off value (194 mg/dL), the patients were divided into two groups: 50 patients with high TC (TC ≥ 194 mg/dL) and 51 patients with low TC (TC < 194 mg/dL). High total cholesterol was significantly associated with increased BMI, tumor size, lymph node metastasis, and tumor grade. However, no significant correlation was observed with age, menopausal status, distant metastasis, hormonal status, histological subtype, or molecular subtype. Table 4 summarizes the comparison of clinicopathological factors according to TC levels:

Table 4: Comparison of clinicopathological factors of breast cancer patients between high TC and low TC groups:

Variables	Category	N	Low TC (<194) (N=50)	High TC (≥194) (N=51)	P-Value
Age (years)	< 40	15	6 (11.8 %)	9(18%)	
	40-60	63	37 (72.5%)	26 (52%)	0.09
	>60	23	8 (15.7%)	15 (30%)	
Menopause	Premenopause	61	28 (54.9%)	33 (66%)	0.25
	Postmenopause	40	23 (45.1%)	17 (34%)	

Variables	Category	N	Low TC (<194) (N=50)	High TC (≥194) (N=51)	P-Value
BMI (Kg/m²)	Normal weight (<25)	33	25 (49%)	8 (16%)	**0.002***
	Over-weight (25-29.9)	43	17 (33.3%)	26 (52%)	
	Obesity (≥30)	25	9(17.7%)	16(32%)	
Grade	Grade1	9	6 (11.7 %)	3(6%)	**0.013***
	Grade2	50	31 (60.8%)	19 (38%)	
	Grade3	42	14(27.5%)	28(56%)	
Tumor size	T1	9	7 (13.7%)	2 (4%)	**0.04***
	T2	62	34(66.7%)	28(56%)	
	T3+T4	30	10 (19.6%)	20 (40%)	
Lymph nodes metastasis	N0	43	31 (60.8%)	12 (24%)	**0.001***
	N1	23	13 (25.5%)	10(20%)	
	N2+N3	35	7 (13.7%)	28 (56%)	
Distant metastasis	M0	97	49 (96.1%)	48 (96%)	0.98
	M1	4	2 (3.9%)	2 (4%)	
ER	Negative	34	16 (31.4%)	18 (36%)	0.62
	Positive	67	35 (68.6%)	32 (64%)	
PR	Negative	52	26 (51%)	26 (52%)	0.91
	Positive	49	25 (49%)	24 (48%)	
HER2	Negative	71	39 (76.5%)	32 (64%)	0.17
	Positive	30	12 (23.5%)	18 (36%)	
Histological types	IDC	87	46 (90.2%)	41 (82%)	0.47
	ILC	9	3 (5.9%)	6 (12%)	
	Others	5	2 (3.9%)	3 (6%)	
Molecular subtypes	Luminal A	51	28 (54.9%)	23 (46%)	0.47
	Luminal B	20	7 (13.7%)	13 (26%)	
	HER2-overexpression	10	5(9.8%)	5 (10%)	
	TNBC	20	11(21.6%)	9 (18%)	

5- Association between NLR and total cholesterol in breast cancer patients:

We evaluated the correlation between total cholesterol levels and NLR using cut-off values. We found that high total serum cholesterol was significantly associated with high NLR in breast cancer patients(**p=0.004**), as shown in Table 5:

Table 5: The association between NLR and total cholesterol in breast cancer patients:

			TC levels		p-value
NLR	Value	N	TC<194 (N=51)	TC≥194 (N=50)	**0.004***
	NLR<2	45	30(58.8%)	15(30%)	
	NLR≥2	56	21(41.2%)	35(70%)	

*P<0.05

6- Association of elevated values of both NLR and total cholesterol with some clinicopathological factors:

We also assessed the correlation between elevated values of the studied markers (NLR ≥ 2 and TC ≥ 194 mg/dL) and clinicopathological parameters. The patient cohort (N = 101) was divided into two groups: Group 1 (N = 35), which included patients with both NLR ≥ 2 and TC ≥ 194 mg/dL, and Group 2 (N = 66), which included the

remaining patients. A statistically significant correlation was found with tumor size (p = 0.01) and lymph node metastasis (p = 0.001). However, no significant correlation was observed with tumor grade or distant metastasis (p > 0.05), as illustrated in Table 6:

Table 6: association between high NLR and total cholesterol with some clinicopathological characteristics in breast cancer patients

Tumor characteristics		Patient group(N=101)		*P*-Value
		Group1(N=35)	Group2(N=66)	0.01*
Tumor size	T1	2(5.7%)	7(10.6%)	
	T2	16(45.7%)	46(69.7%)	
	T3+T4	17(48.6%)	13(19.7%)	
Lymph nodes metastasis	N0	7(20%)	36(54.6 %)	0.001*
	N1	8(22.9%)	15(22.7%)	
	N2+N3	20(57.1%)	15(22.7 %)	
Distant metastasis	M0	33(94.3%)	64(97%)	0.51
	M1	2(5.7%)	2(3%)	
Tumor grade	Grade1	3(8.6%)	6(9.1%)	0.06
	Grade2	12(34.3%)	38(57.6%)	
	Grade3	20(57.1%)	22(33.3%)	

*P<0.05

DISCUSSION

This study evaluated NLR (Neutrophils to Lymphocytes ratio) and total cholesterol in Syrian breast cancer patients. We also assessed WBC, neutrophil, and lymphocyte count. We found significant differences between early-stage and advanced-stage patients. The values were higher in the advanced stage except for lymphocyte count. These findings are consistent with other studies that evaluated the predictive value of NLR in breast cancer. Wiranta *et al.* and Phillip *et al*. found a significant correlation between NLR and breast cancer staging [14][16]. Gong et al. also found an association between high neutrophil count and tumor progression in patients with breast cancer[17]. Lymphocyte count was higher in the early stage similar to the findings of Rana et al. [18].

The inflammatory response has a major role in acerbating different cancers, including breast cancer, by detecting many infilitrating immune cells in malignant tissues[19]. Neutrophils activate tumor progression and invasion through several mechanisms. For example, neutrophils can produce pro-inflammatory cytokines including interleukin-6 (IL-6), IL-7, and IL-8, which induce tumor invasion. They also can secrete circulating vascular endothelial growth factor (VEGF), promoting tumor development. High neutrophil count was associated with poor survival and advanced TNM stage [20][16]. On the other hand, lymphocytic response is considered an important component for controlling cancer progression by producing cytokines such as IFN-ƛ ,which are effective against tumor growth and metastasis [21]. In addition, lymphopenia is associated with adverse consequences in advanced malignancies [22]. All these effects could lead to increasing NLR in peripheral blood. Elevated NLR among breast cancer patients was suggested to be correlated with advanced stage and increasing tumor aggressiveness [23].

Furthermore, our study found an increase of serum total cholesterol in the advanced stage compared to the early stage, which could result from cholesterol composition of tumor cells. According to previous studies, cholesterol synthesis is linked with cancer stem cells, which are cancer cells correlated with tumor progression

and metastasis[24]. Ehmsen et al. showed an augmenting of *de novo* cholesterol synthesis from breast cancer stem cells [25].

We evaluated the clinicopathological characteristics of patients according to NLR and total cholesterol obtained using the ROC curve. High NLR values were significantly associated with increased tumor size and lymph node metastasis. These findings were by Elyasina et al. and Sokmen et al. [26][27]. High neutrophil count induces secreting cytokines and growth factors that promote tumor invasion and angiogenesis[20]. Breast cancer cells also activate the secretion of IL-1β, IL-17, and G-CSF inhibiting CD8 T cells and promoting metastasis[28].In addition, high serum levels of total cholesterol were significantly associated with increased tumor size, lymph node metastasis, tumor grade, and BMI. These results were consistent with previous studies.

Ahmed et al. demonstrated a gradual increase in serum cholesterol levels with increasing tumor size [29]. Jin et al. showed that patients with abnormal blood lipids had a higher rate of positive lymph nodes than patients with normal lipids[30]. Cholesterol has been shown to increase cancer cell development and proliferation through activating AKT phosphorylation[31]. Moreover, 27 hydroxy cholesterol has been found to increase the expression of matrix metalloproteinase9 (MMP9) and activate migration and epithelial-to-mesenchymal transition (EMT) in breast cancer cells [24]. Pandag et al. demonstrated a significant correlation between cholesterol levels and the grade of breast cancer. It has been found that changes in cholesterol levels could affect tumor grading. It could influence the expression of proteins related to advanced tumors in mammals [32]. In addition, 27HC, by activating EMT, could increase tumor grade. Feng et al. showed that the expression of EMT markers had increased with higher tumor grade [33].

There was also a significant correlation between cholesterol levels and BMI in line with Owiredu et al. and Mina et al.[34],[35]. That could result from increasing its synthesis by adipose tissues [36].

High levels of serum total cholesterol were significantly associated with high NLR similar to the finding of Dominguez *et al*. [13]. Also, high values of both were associated with increased tumor size and lymph node metastasis. The alterations in lipid levels, including total cholesterol, can affect immune cell activation. Cholesterol metabolites, such as oxysterols, induce neutrophil recruitment through activating CXC receptor 2(CXCR2). Recruited neutrophils have been found to promote angiogenesis and tumor growth. Furthermore, elevated total cholesterol levels can inhibit T-cell receptor signaling, impairing T-cell proliferation, cytokine production and decreasing anti-tumor immune response [37][10].

CONCLUSIONS

We found a statistically significant difference in NLR and total cholesterol values between patient groups stratified by tumor stage. Higher NLR and total cholesterol levels were associated with more advanced stages of breast cancer. Furthermore, based on the cut-off values determined for both markers using ROC curve analysis (maximizing sensitivity and specificity), a significant correlation was observed with tumor size and lymph node metastasis. Therefore, pretreatment NLR and total cholesterol may serve as predictive markers for breast cancer stage. However, further studies with larger sample sizes are needed to evaluate the prognostic value of these markers, particularly in relation to survival and recurrence rates.

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نسبة العدلات إلى اللمفاويات ومستويات الكوليسترول الكلي قبل العلاج كواسمات حيوية للتنبؤ بعدوانية سرطان الثدي

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ملخص

يعتبر سرطان الثدي من أكثر السرطانات شيوعاً لدى النساء حول العالم. تتواجد مجموعة من العوامل لتي بإمكانها التأثير على عدوانية الورم, من بين هذه العوامل نسبة العدلات إلى اللمفاويات (NLR) ومستويات الكوليسترول الكلي. نتيجة قلة الدراسات التي تقيم العلاقة بين الواسمات السابقة ومرحلة الورم, هدفت هذه الدراسة إلى تقصي دور كل من النسبة NLR ومستويات الكوليسترول الكلي كواسمات حيوية للتنبؤ بمرحلة الورم في سرطان الثدي. قمنا بتقييم 101 من المريضات المُشخصات حديثاً ودراسة علاقة كل من العوامل السابقة مع بعض الخصائص السريرية للمريضات بالاعتماد على القيم الحدية التي تم تحديدها باستخدام منحنى خصائص تشغيل المستقبل ROC curve. أظهرت نتائجنا وجود ارتباط هام بين مرحلة الورم وكل من نسبة العدلات إلى اللمفاويات, الكوليسترول الكلي, الكريات البيض والعدلات ($p<0.05$). بالاعتماد على مرحلة الورم, تم تحديد القيم الحدية 2 لنسبة العدلات إلى اللمفاويات و 194mg/dl للكوليسترول الكلي .ترافق ارتفاع نسبة العدلات إلى اللمفاويات مع تزايد حجم الورم($p=0.004$) ونقائل العقد اللمفية($p=0.021$) بينما ترافق ارتفاع مستويات الكوليسترول الكلي مع ازدياد مشعر كتلة الجسم($p=0.002$) , حجم الورم($p=0.04$), نقائل العقد اللمفية ($p=0.001$) ودرجة الورم($p=0.013$) كما ترافق ارتفاع النسبة NLR مع ارتفاع مستويات الكوليسترول الكلي لدى المريضات, وبالتالي, نسبة العدلات إلى اللمفاويات ومستويات الكوليسترول الكلي قبل العلاج قد تكون عوامل مساعدة للتنبؤ بمرحلة الورم في سرطان الثدي.

الكلمات الدالة: سرطان الثدي، نسبة العدلات إلى اللمفاويات، الكوليسترول الكلي.

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