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Assessment of Interleukin-19 Level and Factors Associated with Breast Cancer for A Sample of Al-Najaf Women, Iraq

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ABSTRACT

Background: *Among women, breast cancer is the primary cause of cancer-related mortality, with a 5-year survival rate after metastases of more than 20%. Therefore, improving early diagnosis is essential to improving the prognosis of the condition. The study aimed to assess Interleukin-19 (IL-19) as a marker in women with breast cancer.*

Materials and methods: *This study is a case-control design conducted at National Hospital for Oncology and Hematology in Najaf and AL-Sadder Medical City Hospital. A convenience sampling of 160 samples. The study comprised two groups including 80 patients with breast cancer, and 80 healthy controls. Five milliliters of venous blood were collected from every individual in the study consecutively, the blood was distributed into gel tubes (6ml). Interleukin-19 (IL-19) were measured by ELISA kit, the biochemical kit used in the study for performed by a company Sun Long Biotech Co, Ltd.*

Results: *The results found that patients had significantly lower mean IL-19 levels (9.814±4.992 Pg/ml) than controls (33.666±11.49 Pg/ml), at statistically significant P.value <0.001. Also, the results found that there was no significant difference between stages (P.value >0.05). At the same time, all stages (0-III) gradually lower mean IL-19 levels compared to healthy controls (P.value <0.001).*

Conclusions: *The present study found that Interleukin-19 levels were lower significantly in women with breast cancer. Furthermore, the results reveal that patients with metastatic BC had significantly lower mean IL-19 levels compared to controls.*

Keywords: *Breast cancer, Interleukin-19, Cancer Stages.*

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INTRODUCTION

A malignant state known as breast cancer (BC) is typified by abnormal growth and unchecked cell division in the breast's lobular units and terminal duct. This may result in the invasion and obliteration of healthy tissue, as well as the spread of malignant cells throughout the body to other parts via the lymphatic system or circulation (1). Breast cancer is categorized depending on a number of factors and for a variety of purposes (2). The primary classifications are histopathological type, tumor grade, tumor stage, and protein and gene expression (2). According to the 2011 World Cancer

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Report, 22.9% of all female instances of invasive malignancies are BC patients. Furthermore, according to a 2015 World Health Organization report, 16% of all malignancies that strike women are breast cancers. It became the most common kind of cancer among women in 2012, accounting for 25% of all diagnosed cases (3).

As a member of the IL-10 family, interleukin-19 is expressed by several kinds of tumor cells. This cytokine's expression in breast cancer has been found in the tumor's later stages. Furthermore, it has been documented to be a factor in an increased rate of cell division and a significant increase in the dissemination of cancer cells to other body regions, leading to a less favorable prognosis (4). Recently, both in vitro and in vivo methods have been used to study the processes linking IL-19 to breast cancer. IL-19 has an autocrine effect on the cells that cause breast cancer. In addition to indirectly fostering the development of breast cancer, IL-19 directly contributes to the proliferation and migration of tumor cells. This suggests that blocking IL-19 may be a potential therapy strategy and that IL-19 may be utilized as a prognostic marker for breast cancer (5).

MATERIALS AND METHODS

Study design and setting:

This study is a case-control design conducted in Najaf province (National Hospital for Oncology and Hematology and AL-Sadder Medical City Hospital). The data was collected during a period from July to November 2023.

The study groups:

A convenient selection of 160 specimens. There were two groups in the study: eighty breast cancer patients and eighty healthy controls. Patients with BC who have had a prior diagnosis from a specialist, according to the doctor. BC disease was chosen after histopathology results confirmed it. Before receiving radiation therapy or chemotherapy, each patient was examined. In contrast, the healthy controls were those who did not use drugs and did not have a medical history of severe or chronic illnesses.

Selection criteria:

Participants in this study must be at least 18 years old (age matched within 2 years between study groups). However, the study did not include subjects with microbial infections, autoimmune diseases, chronic illnesses, or pregnancy. Furthermore, masculine sex was not included.

Methods of sample collection:

After interviewing the members of the study groups, their age, occupation, residence, smoking status were taken using a questionnaire designed by the researcher. After that, 5 millilitres of venous blood were collected from every individual in the study consecutively, the blood distributed into: gel tubes (6ml). The blood in tubes is centrifuged for 10 minutes at 3000 rpm.

Immunological Assays:

Interleukin-19 (IL-19) were measured by ELISA kit, the biochemical kit used in the study for performed by a company Sun long Biotech Co, Ltd (China).

STATISTICAL ANALYSIS:

The statistical program for social sciences (IBM-SPSS) version 27 and Microsoft Office Excel 2010 were utilized to collect, organize, examine, and present the data. The numerical data were presented as mean, standard deviation, and range after the Kolmogorov-Smirnov normality test was performed to

determine whether the variables were normally distributed or not. The least significant difference (L.S.D.) test was computed using ANOVA analysis to determine the statistical significance of the data. P values below 0.05 were considered significant. The L.S.D. values and the mean difference values were compared. Conversely, in the event that the variable exhibits a regular distribution, the mean difference between any two groups was examined using the independent samples t-test. To investigate the relationship between two or more category variables, the chi-square test was used. P-values of 0.05 or less were used to determine the significance level, while 0.01 or less was used to determine the very significant level.

RESULTS

In Figure 1, the results found that there were no significant differences between the percentages of breast cancer patients and healthy controls (p = 0.988).

In table 1, the results found that healthy controls have a higher proportion of employed people compared to patients (16.0% vs. 47.3%) respectively, while breast cancer patients are mostly housewives compared to controls (78.8% vs. 42.5%). Significant professional status differences exist (p < 0.001*). In terms of academic achievement, patients are more illiterate compared to controls (37.5% vs. 16.3%) and healthier controls have more Bachelor's and higher degrees compared to patients (8.8% vs. 36.3%). Significant educational status differences exist (p < 0.001*). Residence also differs, with healthy controls living in urban areas (68.8%) compared to patients (88.8%), while patients in rural areas (31.3%) compared to controls (11.3%). In addition, the present results found that there is a significant difference between patients and controls in terms of smoking status (P=0.029), this explain that patients are more likely to be smokers (11.3%) than control subjects (2.5%).

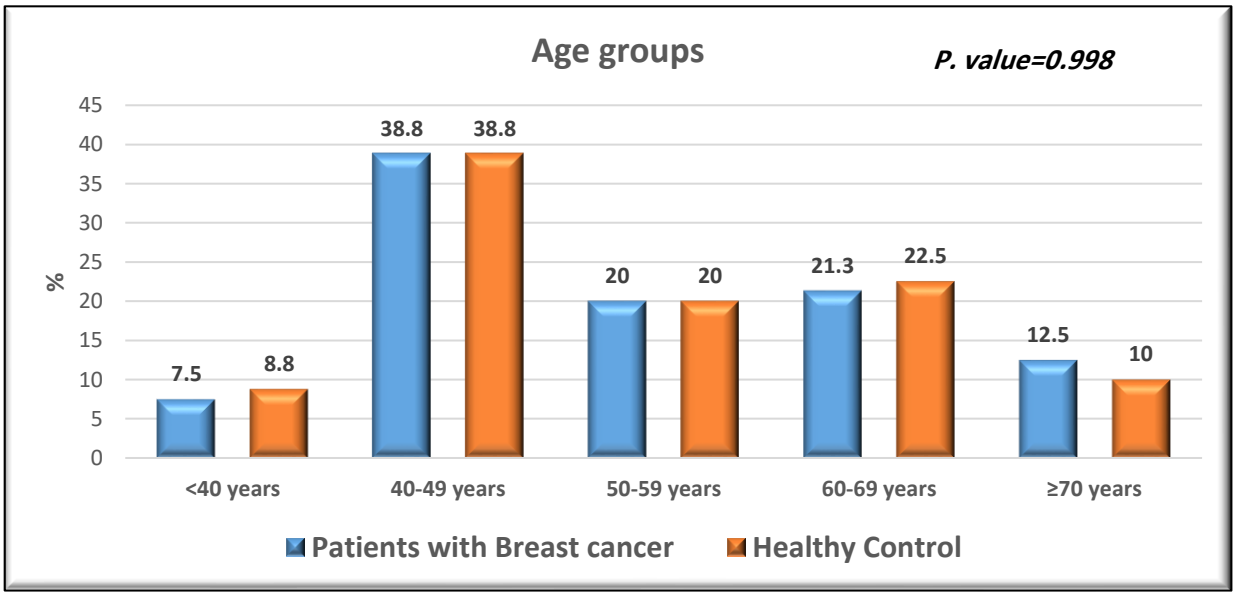

Figure (1): The distribution of the patients and control subjects according to demographic characteristics.

Table (1): The distribution of the patients and control subjects according to some factors.

		Groups				P. value
		Patients with Breast cancer		Healthy Control		
		No.	%	No.	%	
Profession	Employed	12	15.0	37	46.3	**<0.001***
	Housewife	63	78.8	34	42.5	
	Retired	5	6.3	9	11.3	
Academic achievement	Illiterate	30	37.5	13	16.3	**<0.001***
	Primary school	21	26.3	20	25.0	
	Secondary school	11	13.8	1	1.3	
	Diploma	11	13.8	17	21.3	
	Bachelor's and higher	7	8.8	29	36.3	
Residence	Urban	55	68.8	71	88.8	**0.002***
	Rural	25	31.3	9	11.3	
Smoking status	Smoker	9	11.3	2	2.5	**0.029***
	Non-smoker	71	88.8	78	97.5	

In table 2, the results found that patients had significantly lower mean IL-19 levels (9.814±4.992 Pg/ml) than controls (33.666±11.49 Pg/ml), at statistically significant P. value <0.001. Also, the results found that there was no significant difference between stages (P. value >0.05). At the same time all stages (0-III) were gradually lower mean IL-19 levels compared to healthy controls (P. value <0.001). In addition, the results reveal that all patients whether metastatic BC or not had significantly lower mean IL_19 levels compared to controls (P. value<0.001). while there was no significant difference between Metastatic BC and Non-Metastatic BC (P. value >0.05).

In Figure (2) Receiver operator characteristic (ROC) curve analysis was used to assess the interleukin-19 cutoff value and predict breast cancer as diagnostic or adjuvant diagnostic tests. The results are displayed in table (3), and figure (2). With sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the curve, and P. value of 95.0%, 81.3%, 83.5%, 94.2%, 0.969 (0.947-0.991), and <0.001, the interleukin-19 cutoff value was less than 20.01.

Table (2): Comparison between levels of the patients with breast cancer and healthy control according to the Interleukin-19 levels.

Interleukin-19			
Groups	**Mean± SD**	**SE**	**P. value**
Patients with BC	9.814±4.992	0.558	**<0.001**
Healthy Control	33.666±11.49	1.285	
Stage 0	7.980±3.932 A	1.015	**<0.001**
Stage I	10.399±5.431 A	1.214	
Stage II	10.708±5.800 A	1.297	
Stage III	9.731±4.468 A	0.894	
Healthy Control	33.666±11.490 B	1.285	
Metastatic BC	9.362±4.932 A	0.834	**<0.001**
Non-Metastatic BC	10.165±5.065 A	0.755	
Healthy Control	33.666±11.490 B	1.285	

A significant difference between two independent means using Students-t-test at 0.05 level.

(*) Two independent sample test. (#) Analysis of variance (ANOVA); using least significant differences as post hoc test (LSD); Different letter denotes to significant differences less than 0.05.

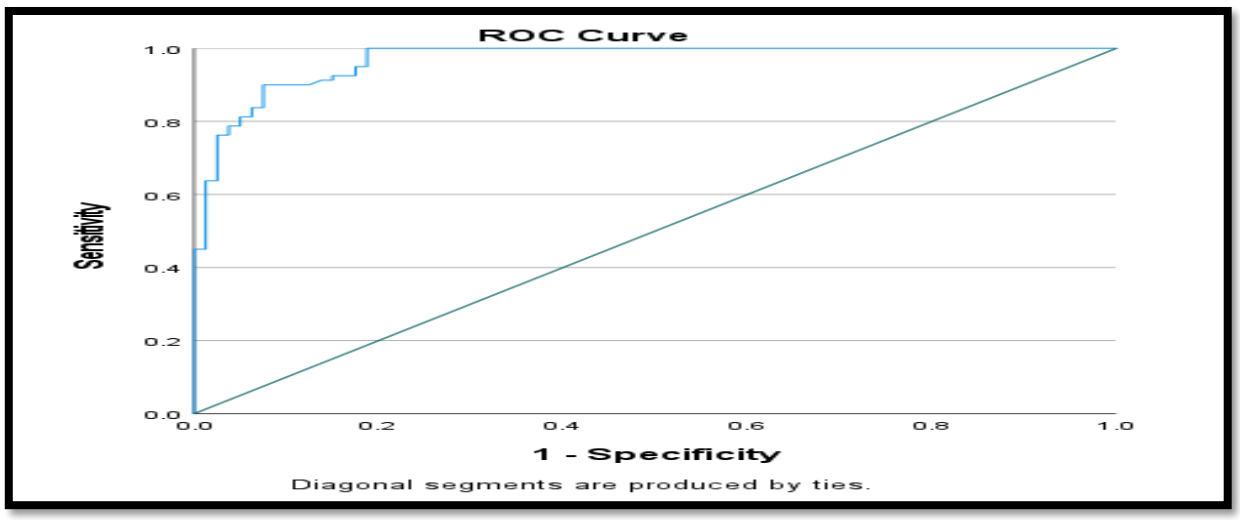

Figure (2) : Roc curve of IL-19 level in patients with breast cancer.

Table (3): Sensitivity and specificity of interleukin-19 level in patients with breast cancer.

ROC Analysis (Cutoff Point =20.1)			Group	
			Patients	Control
IL-19	Predictive-Patients <20.1	No.	76	15
		%	95.0%	18.8%
	Predictive-Control ≥20.1	No.	4	65
		%	5.0%	81.3%
	Sensitivity %	95.0 %		
	Specificity %	81.3 %		
	PPV %	83.5 %		
	NPV %	94.2 %		
	AUC (95% CI)	0.969 (0.947- 0.991) **"Excellent"**		
	P. value	<0.001*		

DISCUSSION

In this study, breast cancer patients are primarily housewives. In line with the findings of (6), reported that housewives had higher chances of breast cancer (OR = 1.37 (95% CI 0.98 to 1.91)). Numerous factors increase housewives' breast cancer risk. First, busy housewives may struggle to exercise and receive regular exams, delaying symptom detection and prevention. Economic factors may also play a role, since lower-income families have less access to healthcare and breast cancer screening and prevention information. Unaided housework may weaken immune systems and induce hormone imbalances, increasing cancer risk. In this study, it was discovered that poor education was linked to breast cancer. These findings confirmed the Iranian research (7) that found greater education was associated with decreased breast cancer risk [OR 0.17, 95% CI 0.06-0.45]. These findings agreed with the previous research (8) that linked low education to breast cancer. We can discuss that lower-educated persons have a higher risk of breast cancer for several reasons. First, limited access to healthcare and preventative programs may delay breast cancer detection in this population. Socioeconomic disadvantages include poor food, limited physical exercise, and higher smoking and alcohol consumption enhance breast cancer risk, as does lower educational attainment. Lower-educated persons may also be unaware of healthy lifestyle choices and screenings and self-examinations, missing early intervention opportunities.

The results of this study indicate that breast cancer was higher in patients who live in rural areas compared to controls. This result

disagreed with the study findings done by (9) which reported that rural women living have lower incidence of breast cancer compared to women in urban areas. Also, (9) reported that rural women have lower use of screening mammography and are more likely to have a late stage breast cancer diagnosis. Women in rural areas experience substantial barriers to accessing high quality diagnostic care and treatments. According to (10) Rural populations are not at increased risk for developing breast cancer. The possible reason for this difference from previous studies may be the result of the difference in research methodology and may also be the result of providing health services in rural and urban areas differently between countries.

The study also found that rural patients had higher breast cancer rates than controls. This contradicted (9) results indicating rural women had a lower breast cancer rate than metropolitan ones. Also, same study reported that rural women utilize less screening mammography and are more likely to be diagnosed with late-stage breast cancer (9). Rural women face significant challenges to high-quality diagnosis and treatment. (10) found no higher breast cancer risk in rural areas. Due to research methodology and rural/urban health care delivery differences across nations, this study may vary from prior ones.

In this study, smoking status was related to increase breast cancer. This result is in agreement with the study findings conducted by (11), which found that smokers had higher risk of premenopausal breast cancer (AOR=1.75; 95% CI: 1.04–2.94). In addition, a study by (12) reported that smoking is associated with an increased incidence of hormone receptor positive breast cancer. Also, these results agreed with (13) which revealed that smoking (active and passive) increases the risk of BC in women. This can explain that smoking is a known breast cancer risk for several reasons. Smoking introduces polycyclic aromatic hydrocarbons and aromatic amines, which damage DNA and increase cancer risk. Smoking also disrupts hormone levels, notably estrogen, which is critical to breast cancer formation. Prolonged exposure to high estrogen levels may fuel breast cancer cell growth. Smoking also causes inflammation and weakens the immune system, making tumor growth easier (14) (15).

The current results found that patients had significantly lower mean IL-19 levels than controls, at statistically significant P. value <0.001. Also, these results found that all stages (0-III) were gradually lower mean IL-19 levels compared to healthy controls. in addition, all patients whether metastatic BC or not had significantly lower mean IL_19 levels compared to controls (P. value<0.001). These results were compatible with the study findings conducted in Iran (16), which found that there were significantly lower serum interleukin-19 levels in breast cancer patients compared to healthy controls. Compared to the healthy control group, the decrease in serum interleukin-19 concentration was seen in all patients with breast cancer. Another finding of this study which could support this hypothesis was a significantly decreased serum level of IL-19 in patients compared to normal controls (4). While these results disagreed with (17) which found that elevated IL-19 linked with metastasis in breast cancer. This can be explanation for decreased IL-19 concentrations in patients with breast cancer can be the recruitment of a part of IL-19 systemic sources to the tumor site, so whether IL-19 producing monocytes and B cells are recruited from the periphery to the tumor site is another possibility worth evaluating (16).Other explanations, low IL-19 levels in breast cancer patients may be caused by many reasons. First, cancer patients' immune system dysregulation commonly alters cytokine profiles, lowering IL-19 levels (18). Second, tumor cells may impede immune cell activity or induce immunosuppressive substances to

reduce IL-19 synthesis. Cancer-associated inflammation and immune evasion may alter cytokine signaling pathways, which may not encourage IL-19 expression in the tumor microenvironment (19). In breast cancer patients, genetic variants or epigenetic alterations in the IL-19 gene or its regulatory regions may lower its expression (20).

CONCLUSIONS

The present study found that Interleukin-19 level were lower significantly in women with breast cancer. Furthermore, the results reveal that patients with metastatic BC had significantly lower mean IL-19 levels compared controls. Furthermore, smoking status, live in rural areas, housewife, and low education were associated with breast cancer.

Ethical approval

Under the reference number MEC-56, dated September 20 (09/2023), the study was carried out in accordance with a protocol that was approved by a local ethics committee at University of Kufa/ Medicine College/department of medical microbiology and AL-Najaf Health Directorate.

Authors' contributions

Each author took part in the planning and writing of the manuscript as well as coordinating the data preparation. The final draft of the manuscript was read and approved by the author.

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