

## Comparison of Clinicopathological Features between Premenopausal and Postmenopausal Female Breast Cancer Patients in Kurdistan Region of Iraq: A Retrospective Single Institution Study of 671 Female Patients

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### KEYWORDS

Breast cancer, Epidemiology, Menopausal status, Lymphovascular invasion, Stage at diagnosis.

### ABSTRACT

**Introduction:** Breast cancer is the most common cancer in women, and its incidence is increasing annually worldwide. It accounts for 24% of new cancer cases and 15% of cancer deaths in 2018, and according to the GLOBOCAN Cancer Tomorrow prediction tool, incident cases are expected to increase by more than 46% by 2040. Studies carried out thus far have shown that risk factors and histopathological features of breast malignancies may vary among different age groups. Menopausal status is an essential factor influencing clinicopathological characteristics of patients with breast cancer. Prognostic factors are used to estimate how aggressive the tumor may evolve and to decide on a treatment approach. In Iraq, breast cancer is most frequently seen in younger women in their fourth and fifth decades of life, who often show in advanced stages at the time of diagnosis, according to previous surveys.

**Objectives:** The main objective of this study was to assess the clinicopathologic features between premenopausal and postmenopausal breast cancers to provide valuable insights into what may influence the age at diagnosis of breast cancer in the Kurdistan region of Iraq.

**Methods:** This retrospective study included 671 non-metastatic breast cancer patients referred to Zhianawa Cancer Center between January 2015 and December 2017. Disease stage was determined using the American Joint Committee on Cancer and Union for International Cancer Control (UICC) ("Tumour," "Nodes," "Metastases") TNM systems. The patients were divided into premenopausal and postmenopausal groups. The chi-square test was used to evaluate the association between the variables.

**Results:** The mean age of the participants was 47.5 years. The most prevalent age group was 40-49, followed by the age group 50-59. Of the participants, 60.5% were premenopausal, and 39.4% were postmenopausal. Stage IIIA was the most common stage at diagnosis. At the same time, the most minor stage at diagnosis was stage 0. The second most common stage was IIB. There was a strong association between menopausal status with grade (P value 0.001) and LVI (P value 0.01); however, there was a non-significant correlation between menopausal status and stage at diagnosis (P value 0.529).

**Conclusion:** Most patients included in this study had locally advanced disease stages. Menopausal status affected grade and LVI but not stage. Further professional efforts, endorsed by practical policy decisions, are recommended to down stage breast cancer through promoting evidence based protocol guidelines and adopting comprehensive well designed diagnostic, screening and cancer control strategies.

### 1. Introduction

Breast cancer is the most common cancer in women, and its incidence is increasing annually worldwide. It accounts for 24% of new cancer cases and 15% of cancer deaths in 2018, and according to the GLOBOCAN Cancer Tomorrow prediction tool, incident cases are expected to increase by more than 46% by 2040 [1].

Breast cancer is responsible for approximately 40000 deaths each year in the United States. Metastasis is the most common cause of breast cancer deaths [2]. Despite the advances, 20-30% of patients with early breast cancer will experience relapse, presenting with distant metastatic disease [3]. Indeed, 6-10% of patients show metastatic disease at the initial diagnosis of breast cancer [4]. The risk of recurrence is primarily affected by the stage at initial presentation and the biological features of the tumor. Tumor size, nodal involvement, grade, lymphovascular invasion, and estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status are all independent risk factors for relapse [5,6].

Breast cancer is a heterogeneous disease, divisible into various clinical subtypes, and the pathogenesis is not clear [7]. As early as the 1970s, De Waard proposed the concept that breast cancers develop by two distinct pathways, each with a different age-specific incidence rate curve [8]. The first pathway results in mainly premenopausal tumors with peak occurrence early in life. The second pathway results in predominantly postmenopausal cancers with peak incidence later in life, similar to late-onset estrogen receptor(ER)-positive

cancers [9].

Studies carried out thus far have shown that risk factors and histopathological features of breast malignancies may vary among different age groups [10]. Menopausal status is an essential factor influencing clinicopathological characteristics of patients with breast cancer. Prognostic factors are used to estimate how aggressive the tumor may evolve and to decide on a treatment approach [11,12].

In Iraq, breast cancer is most frequently seen in younger women in their fourth and fifth decades of life, who often show in advanced stages at the time of diagnosis, according to previous surveys [13]. To treat the illness sooner rather than later, Iraq launched a national program for early detection of breast cancer in 2000. The International Agency for Research on Cancer (IARC) then supervised the establishment of a National Breast Cancer Research Program in 2010 to underline the importance of research as one of the fundamental pillars in the adoption of a national cancer control strategy [14].

The main objective of this study was to assess the clinicopathologic features between premenopausal and postmenopausal breast cancers to provide valuable insights into what may influence the age at diagnosis of breast cancer in the Kurdistan region of Iraq.

## 2. Material and methods

This study is a retrospective cohort study of breast cancer patients referred to Zhianawa Cancer Center (ZCC), which is a regional tertiary cancer center in Sulaymaniyah in the Kurdistan region of Iraq. A total of 976 breast cancer patients had been referred to ZCC between January 2015 and December 2017. One hundred ninety-five patients were excluded from the study either because they were metastatic (ninety-five) or recurrent (thirty-seven) or with synchronous malignancies (fifteen) and male sex (five). Also, 110 patients were excluded because they did not have complete medical records. A total of 671 patients were included in this study. Inclusion criteria were female, aged 18 and above, nonmetastatic breast cancer at diagnosis, pathological confirmation of diagnosis, and complete patient records. We used patients' medical records documents and digital health records, which included demographic variables (age at diagnosis, menopausal status, and residency) and clinicopathological features (histological subtype, tumor size, stage groups, grade, Lymphovascular invasion (LVI)).

Joint Committee on Cancer (AJCC) guidelines and histological grading were performed according to the Nottingham grading system. LVI invasion were assessed by histopathological examination using hematoxylin and eosin staining.

Stata/MP version 14.2 is used for statistical analysis. The chi-square test was used to assess the association between menopausal status and grade, LVI, and stage groups. A p-value of less than 0.05 was considered statistically significant.

The Research Protocol Ethics Committee at Kurdistan Higher Council of Medical Specialties approved this study protocol numbered (1973) on (26 November 2023).

## 3. Results

A total of 671 patients were included and analyzed in this study. The mean age of the participants was 47.5 years. Patient demographic and clinicopathological features are shown in Table 1. Invasive carcinoma comprised the vast majority of histological subtypes, making 92.6% of cases, while only eight patients had in situ disease. Other carcinomas made up 6.12% of the patients. The most prevalent age group was 40-49, followed by the age group 50-59. Of the participants, 60.5% were premenopausal, and 39.4% were postmenopausal. Stage IIIA was the most common stage at diagnosis. The second most common stage was IIB. At the same time, the least stage at diagnosis was stage 0. Table 1 contains detailed demographic and clinic pathological information of the participants.

**Table 1: Baseline characteristics of the participants (n=671)**

Baseline characteristics	N	%
Tumor histology		
Insitu carcinoma	8	1.19
invasive carcinoma	622	92.69
other carcinomas	41	6.12

Stage at diagnosis		
Stage 0	8	1.19
Stage IA	62	9.24
Stage IIA	140	20.86
Stage IIB	148	22.06
Stage IIIA	171	25.48
Stage IIIB	16	2.38
Stage IIIC	126	18.78
Ten year age interval		
20-29	22	3.28
30-39	134	19.97
40-49	250	37.26
50-59	172	25.63
60-69	72	10.73
70-79	18	2.68
80	3	0.45
Menopausal status		
Postmenopausal	265	39.49
Premenopausal	406	60.51
Grades		
Grade I	122	28.46
Grade II	348	50.67
Grade III	201	30
LVI		
Negative	295	43.96
Positive	376	56.03
	Mean	Std. Err.
Age_at_diagnosis	47.59762	0.413717
		Interval
		48.40995

Chi-Square test was used to evaluate the association of menopausal status with a stage at diagnosis, grade, and LVI. The association between menopausal status and stage at diagnosis was not significant (Chi-Square test p-value: 0.89). The correlation of menopausal status with histologic grade and LVI was strongly significant, with P values of 0.001 and 0.01, respectively (Table 2).

**Table 2: Association between menopausal status and clinicopathological features.**

Variable	Total		premenopausal		Postmenopausal		P Value
	n	%	N	%	n	%	
Stage							0.89
Stage 0	8	1.2	3	0.4	5	0.7	
Stage IA	62	9.2	40	6	22	3.3	
Stage IIA	140	20.9	84	12.5	56	8.3	
Stage IIB	148	22.1	89	13.3	59	8.8	
Stage IIIA	171	25.5	103	15.4	68	10.1	
Stage IIIB	16	2.4	10	1.5	6	0.9	
Stage IIIC	126	18.8	77	11.5	49	7.3	
Grade							0.001
Grade I	122	28.46	39	9.61	56	21.13	
Grade II	348	50.67	212	52.22	145	54.72	
Grade III	201	30	155	38.18	64	24.15	
LVI							0.01
Positive	295	43.96	227	55.91	103	38.87	
Negative	376	56.03	179	44.09	162	61.13	

#### 4. Discussion

This retrospective study was done on 671 breast cancer patients from the Kurdistan region of Iraq. The mean age at diagnosis in this study was 47.59 years. Similar findings have been reported in Pakistan and China [15, 16]. At the same time, higher mean ages were documented in Turkey and USA, respectively [17, 18].

In this survey, premenopausal cases comprised 60.5% of the total cases. Incidence rates for breast cancer differ among countries and regions around the world. The main reasons for this variety are development status and income, as shown in (Table 3). For example, in developing regions like Middle Africa and Western Asia, the majority of patients are premenopausal, in contrast to Europe and Northern America, where post-menopausal cases compose the vast majority of the patients. Similarly, in countries that have very high and high Human Development Index (HDI), postmenopausal cases compose the majority of the cases, whereas premenopausal cases are the most commonly diagnosed breast cancer cases in low HDI countries [19].

**Table 3: Global estimated number of cases and percentages for premenopausal and postmenopausal breast cancer in 2018**

Region	Premenopausal Cases	Premenopausal Cases (% of total cases)	Postmenopausal Cases	Postmenopausal Cases (% of total cases)
Africa				
Eastern Africa	21085	52.3%	19225	47.7%
Middle Africa	8358	57.7%	6128	42.3%
Northern Africa	24774	45.9%	29143	54.1%
Southern Africa	5148	34.7%	9672	65.3%
Western Africa	25016	55.4%	20141	44.6%
Asia				
Eastern Asia	168915	35.4%	307594	64.6%
Southeastern Asia	51375	37.4%	86139	62.6%
South-central Asia	97872	40.6%	143205	59.4%
Western Asia	24002	42.9%	31912	57.1%
Europe				
Central and eastern Europe	29834	20.0%	119190	80.0%
Northern Europe	16161	19.2%	68111	80.8%
Southern Europe	25853	21.6%	93724	78.4%
Western Europe	31512	18.6%	138128	81.4%
North America	45595	17.40%	216752	82.60%
HDI				
Very high HDI countries	189184	20.7%	723285	79.3%
High HDI countries	236064	35.4%	430667	64.6%
Medium HDI countries	160899	39.9%	241901	60.1%
Low HDI countries	58265	55.2%	47355	44.8%

In our sample, the association of menopausal status with stage was nonsignificant. At the same time, the association between grade and LVI was statistically significant. Several studies have investigated the same association in different populations. It is expected to see a significant association between menopausal status and grade and LVI [16,17]. However, mixed findings have been reported concerning the association between menopausal status and stage at diagnosis. For example, two studies with large sample sizes from China and the USA concluded a significant association [17,20 ]. Similar to our study, research on small sample sizes from Egypt and Pakistan failed to show a statistically significant correlation [15, 21]. However, a comparable survey regarding sample size from Turkiye reported a significant correlation [22]. Table 4 summarizes some selected studies investigating the association between menopausal status and stages done in various regions of the world.

**Table 4: Selected studies on the association**

Author	Country	Sample size	Result
O. Ayodele et al. 2016	Ireland	497	significant
Louise A. et al. 2008	USA	387,231	significant
Humera M. et al 2016	Pakistan	381	nonsignificant
Elsayed A. et al 2014	Egypt	258	nonsignificant
Servet K. et al.	Turkey	428	significant
Ozan U. et al.	Turkey	3325	significant
Fan F. et al.	China	15,389	significant
present studt	Iraq	671	non significant

Lymphovascular invasion (LVI) and histological grade are significant prognostic factors in breast cancer. LVI refers to cancer cells within the lymphatic and/or blood vessels, which means a higher probability of cancer spreading to lymph nodes or distant sites. It is commonly associated with more aggressive tumors and is an important prognostic factor and hence affecting treatment strategies. The risk of recurrence and metastasis are higher in cases with positive LVI status, and it is often seen in more advanced-stage cancers [23].

Histological grade, on the other hand, reflects how much the cancer cells resemble normal breast cells. It is determined based on the degree of differentiation of the tumor cells and their growth patterns. Breast cancers are typically classified into three grades: Grade I (well-differentiated), Grade II (moderately differentiated), and Grade III. Higher histological grades are associated with faster-growing and more aggressive cancers. Studies have shown that tumors with higher grades, such as Grade III, tend to have a worse prognosis compared to lower-grade tumors [24].

Breast cancer in Iraq presents unique epidemiological characteristics compared to other regions. The median age of diagnosis in Iraqi women is around 49 years, with a significant proportion of patients being diagnosed before the age of 50, indicating a younger population affected by this disease [25]. Studies show that approximately 45-54% of patients are younger than 50, which is significantly higher compared to Western countries [26]. The most common age group affected is between 40 and 49 years. A concerning pattern is a late-stage diagnosis, with a substantial proportion of cases diagnosed at stages III or IV when treatment options are less effective [27,28]. For instance, one study found that 40.5% of patients presented at advanced stages [28], and another highlighted that over 65% of cases were stage III or IV at presentation. This late detection is likely related to the absence of routine screening programs and limited public awareness. Such factors [25].

The strength of this research is that, to our knowledge, this is the first study to assess the association of menopausal status with clinicopathological features in Iraqi breast cancer patients. The limitations of this study were the relatively small sample size and the inclusion of data from a single institution.

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