

# HISTOPATHOLOGICAL AND BIOLOGICAL BEHAVIOR OF BREAST CANCER IN ELDERLY KURDISH WOMEN



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## ABSTRACT

### *Background*

Breast cancer is the most prevalent cancer in women, with incidence and mortality increasing markedly with age.

### *Objective*

This study aimed to determine the clinicopathological features and biological behaviors of breast cancer patients in elderly Kurdish women.

### *Materials and Methods*

We retrospectively evaluated the clinicopathological and biological features of breast cancer in elderly Kurdish women ( $\geq 65$  years;  $n = 143$ ) between 2015 and 2021. This cross-sectional study was carried out at the Hiwa haematology-oncology hospital in the Iraqi Kurdistan province of Sulaymaniyah. According to age, patients were divided into groups 1 (65–74 years,  $N=112$ ) and 2 (75 years or older,  $N=31$ ). Clinicopathological characteristics including tumor histology, histological grade, estrogen (ER) and progesterone (PR) and human epidermal growth factor 2 (HER2) status, molecular subtypes, tumor sizes (T), lymph node status (N), lymphovascular invasion (LVI), distant metastasis (M), clinical stage, and tumor focality with laterality were all assessed.

### *Results*

The mean age of the study population was 71.4. The most common histopathological type of breast cancer was invasive ductal carcinoma, followed by invasive lobular carcinoma and papillary carcinoma. Hormone receptor positivity rates were high, and the HER2 status was mostly negative. Luminal A and B (79.7%) were the most frequent types; triple negative (15.2%) was high. The mean age was 72.3 for group 1 (range 65-74) and 84.9 for group 2 (range 75 and older). Excluding symptomatic presentation, progesterone receptor status, and metastasis category, no statistically significant difference was found between the two groups. At the time of presentation, every patient in group 2 had symptoms ( $p=0.047$ ).

### *Conclusion*

Our study results showed that breast cancer in the elderly ( $\geq 65$  years) patients in Kurdish seemed to have more aggressive clinical, pathological, and biological characteristics than older women worldwide.

**Keywords:** *Clinicopathological, Breast cancer, Elderly Kurdish women.*

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## **INTRODUCTION**

Breast cancer is the most common cancer diagnosed in women, accounting for more than 1 in 10 new cancer diagnoses each year. It is the second most frequent cancer-related death among women worldwide <sup>(1)</sup>. The main risk factor for breast cancer is growing older. Over 40% of women with newly diagnosed breast cancer are 65 years or older, and the median age at diagnosis for breast cancer is almost 60 years <sup>(2)</sup>. Elderly people are defined chronologically as those at least 65 years old in most developed nations. However, many developing nations may find it challenging to apply this criterion <sup>(3)</sup>. The number of breast cancer diagnoses in older women is expected to rise by 30% over the next ten years as the US population ages <sup>(4)</sup>. Breast cancer death rates have decreased over time due to advancements in screening and medicines with a therapeutic purpose. However, the survival rate for older women who are diagnosed with breast cancer has not much improved <sup>(5)</sup>.

Most breast cancer screening programs exclude people above the age of 70 due to considerations such as higher non-compliance with therapy, the presence of comorbidities that can increase mortality, and the high expense of the treatment. As a result, breast cancer in elderly individuals is frequently diagnosed more lately. Approximately 48% of patients older than 65 have metastases at the time of diagnosis <sup>(6)</sup>. The risk of death from breast cancer is higher in older people than in younger women <sup>(6)</sup>, and over half of breast cancer deaths happen in women who are 70 years or older <sup>(7)</sup>. Breast cancer in older women has a more favorable phenotype, with a lower-grade carcinoma, less lymphovascular invasion, a high rate of ER and PR positivity, and a low rate of HER2 overexpression. Only a small portion of those patients have triple-negative disease. However, they have larger tumor sizes, involve more lymph nodes, and develop stage IV metastatic disease more frequently <sup>(8)</sup>.

Most tumors have ER and PR expression and lack HER2 overexpression <sup>(9)</sup>. Age does not affect notably the histologic features of breast cancer. Ductal histology remains the most common histology in older patients. However, lobular carcinomas and carcinomas that tend to have more favorable prognoses, such as mucinous and papillary carcinomas, are slightly more common in older patients. These are usually small, proliferating, low-grade tumors <sup>(10)</sup>. Breast cancer in the elderly is linked to features that have an immediate impact on the treatment approach. For instance, older women are

frequently diagnosed at an advanced stage due to under-screening <sup>(11)</sup>, higher prevalence of hormonal positive receptors, higher comorbidity rate, and progressive decline in the functional reserve of multiple organs with age, poor financial and social background, and limited access to transportation <sup>(12)</sup>.

## **MATERIALS AND METHODS**

### **Study population**

This cross-sectional study was conducted at the Hiwa haematology-oncology hospital in the Sulaymaniyah province of Iraqi Kurdistan. In total, 2631 women patients with breast cancer were diagnosed and admitted to Hiwa Hospital from January 2015 to December 2021. Among these patients, 296 cases (11.3%) were 65 years and older at the time of diagnosis. A total of 143 who fulfilled the criteria participated in the study. The selection criteria of the case group were: (i) female gender with age 65 years and older, (ii) Kurdish nationality, (iii) pathologically confirmed of breast cancer between “January 1<sup>st</sup>, 2015 to December 31<sup>st</sup>, 2021.

The data were retrieved through the direct questioning of the patients, which included age, age at diagnosis, residency, marriage status, parity, family history of breast cancer and other cancer, previous personal history of breast cancer and other cancers, history of chronic illness, diagnostic method, the time between the feeling of the lump and diagnosis, type of symptoms at presentation, type of surgical procedure and subsequent treatments, locoregional recurrence after surgery.

Histopathological and biological data were retrieved through a review of histopathology reports. The following data were collected: tumor size, laterality and focality of the mass, histological subtype, histological grades for invasive carcinoma, presence of lymphovascular invasion (LVI), lymph node status, and results of an immunohistochemical study of the biological markers, namely (estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67). The primary method for tissue acquisition in stage IV patients was percutaneous core needle biopsy.

Patients were classified into two groups according to age: Group 1 (65–74 years, N = 112) and Group 2 (75 years or over, N = 31). Clinicopathological features, including tumor histology, histological grade, ER and PR, HER2 status, molecular subtypes, tumor sizes (T),

lymph node status (N), LVI, distant metastasis (M), clinical stage, and tumor focality with laterality, were evaluated.

### **Ethics declaration**

This research was conducted after obtaining permission from the Directorate of Health-Sulaymaniyah along with the Hiwa hematology-cancer Hospital directorate. The Ethics Committee of the College of Medicine University of Sulaymaniyah approved this study. The participants provided informed consent.

### **Statistics**

Data entry was performed using an Excel spreadsheet. Then, the statistical analysis was performed using the SPSS program, version 21 (IBM SPSS Statistical Package for Social Sciences)—the data presented in tabular forms showing the frequency distribution of different variables. Chi-square tests were used to compare the categorical data between different qualitative variables of the study. The use of Kolmogorov-Smirnov and Shapiro-Wilk tests showed a non-normally distributed pattern. P values of 0.05 were used as a cut-off point for the significance of statistical tests.

## **RESULTS**

The mean age of the study population was 74.9 years (minimum-maximum: 67-94), and the mean age at diagnosis was 71 years (minimum-maximum: 65-91). Demographic properties are illustrated in Table 1.

The mean age for group 1 was (72.3); the age range for this group was (65–75); while the mean age for group 2 was (84.88); the age range for this group was (76 years and older). There were 112 patients in group 1 (78.3%) and 31 (21.7%) in group 2.

The number of females with at least one comorbidity was 113 (79%), with hypertension being the most common illness, followed by diabetes mellitus. Comorbidities are shown in Table 2.

As to the detection method, most of the tumors discovered by the patient are herself or their relatives, consisting of 131 patients (91.6%). Only 12 (8.4%) females were asymptomatic at the time of presentation and diagnosed through imaging or a health professional.

### **Histological subtypes**

The histological subtype was analyzed in 143 patients who participated in this study. The most frequent

histological subtype was invasive ductal carcinoma, which accounts for approximately 108 cases (75.5%). In addition, the second most frequent histological type was invasive lobular carcinoma, which account for nearly 20 cases (14%). Papillary carcinoma was the third most frequent histotype, with only 5 cases (3.5%), and the other less frequent histotypes are shown in Table 3. The histological subtypes show no significant difference between the two groups ( $p=0.55$ ) Table 5; however, the lobular subtype and other rare subtypes are slightly more common in group 1.

### **Tumor size, number, and location**

The tumor size, number, and location were analyzed in our study. T categories of the 136 cases were as follows: Tis in only 2 cases (1.4%), T1 in 39 cases (27.3%), T2 in 77 cases (53.8%), T3 in 8 cases (5.6%), and T4 in 10 cases (7%) but T category of 7 cases (4.9%) were unknown (Table 3). The tumor size distribution between the two groups shows no significant difference ( $p = 0.21$ ; Table 5). Regarding tumor focality, there were 118 cases (82.5%) with single tumors, while there were 13 cases (9.1%) with multifocal tumors and 12 cases (8.4%) with multicentric tumors. Tumour laterality in our study showed that the left breast was involved in 73 cases (51%), the right breast was involved in 65 cases (45.5%), and both sides were involved in only 5 cases (3.5%) (Table 3). In addition, there are no significant differences between group 1 and group 2, as shown in Table 5, about tumor focality and laterality ( $p=0.19$  for tumor focality,  $p=0.47$  for tumor laterality).

### **Histological grade**

Histological grading of breast cancer was determined according to the criteria established by Elston and Eliis, which was classified into grades I, II, and III. Histological grading was as follows: grade I in 15 cases (10.5%), grade II in 77 cases (53.8%), grade III in 50 cases (35%), and only 1 case (0.7%) was unknown (Table 3). Furthermore, no significant difference exists between group 1 and group 2 ( $p=0.25$ ; Table 5).

### **Lymphovascular invasion**

In our study, in a total of 143 older women, the lymphovascular invasion was present in 48 cases (33.6%), was not present in 78 cases (54.5%), and was uncertain in 17 cases (11.9%) (Table 3). Regarding lymphovascular invasion, there are no significant differences in distribution between group 1 and group 2 ( $p=0.97$ ; Table 5).

**Lymph node metastasis status**

The lymph node status was analyzed after the exclusion of cases with pathological stage M1 at the time of diagnosis; in a total of 128 cases, regional lymph node involvement at diagnosis was present in 63 (49.2%) of older women with breast cancer, while there was no involvement in 61 cases (47.7%), and unknown in 4 cases (3.1%) (Table 3). In addition, there are no significant differences between groups 1 and 2 (p=0.68; Table 5).

**Biological markers**

In our study, we identified biological markers in 138 of the cases. ER and PR expression and HER2 overexpression or amplification were demonstrated in 108 (75.5%), 98 (68.5%), and 23 (16.1%) of the older women, respectively. They are illustrated in Table 3. There is no significant difference between group 1 and group 2 for ER status (p=0.06; Table 5). However, the PR status between the two groups shows a significant difference (positive: 74.1% vs. 48.4%; negative: 23.2% vs. 45.2%, respectively; p=0.01; Table 5). About HER2 status, there are no significant differences between groups 1 and 2 (p=0.64; Table 5). In our study, molecular phenotypes of 138 older women were as follows:

luminal A in 61 cases (44.2%), luminal B in 49 cases (35.5%), HER2 over-expression in 7 cases (5.1%), and triple-negative in 21 cases (15.2%). Molecular subtypes are shown in Table 4. The distribution of molecular subtypes in group 1 vs group 2 shows no significant difference (p=0.07; Table 5).

**Distant metastasis**

In our study, in 143 cases, distant metastasis was found in 15 (10.5%) patients at the time of diagnosis, while in 128 (89.5%) patients, there were no distant metastases at the time of diagnosis. However, 4 cases (2.8%) later developed metastases (Table 3). About the M category distributions, there are significant differences between group 1 and group 2 (p= 0.004; Table 5)

**Tumor staging**

In our study, in a total of 143 cases, tumor stage distribution was as follows: stage 0 in 2 cases (1.4%), stage I in 25 cases (17.5%), stage II in 65 cases (45.5%), stage III in 29 cases (20.3%), stage IV in 19 cases (13.3%). However, the stage was unknown in only 3 cases (2.1%), as shown in Table 3.

**Table 1. Sociodemographic characteristics of study participants**

Sociodemographic		Frequency	%
<b>Age(Years)</b>	Mean ± SD	74.9 ± 6.4	
	65 - 74	75	52.4%
	75 - 84	54	37.8%
	85 - 94	14	9.8%
<b>Age at diagnosis(Year)</b>	Mean ± SD	71.4 ± 6.0	
	65 - 74	106	74.1%
	75 - 84	29	20.3%
	≥ 85	8	5.5%
<b>Residency</b>	Urban	100	69.9%
	Semi-urban	41	28.7%
	Rural	2	1.4%
<b>Marital status</b>	Unmarried	1	0.7%
	Married	107	74.8%
	Widow	35	24.5%
<b>Total</b>		143	100.0%

**Table 2. Comorbidity diseases of study participants**

<b>Chronic disease</b>		<b>Frequency</b>	<b>%</b>
<b>Hypertension</b>	Yes	101	70.6%
	No	42	29.4%
<b>Diabetes mellitus</b>	Yes	55	38.5%
	No	88	61.5%
<b>Other chronic diseases</b>	IHD	23	3.5%
	Thyroid disease	5	16.1%
	CVA	3	2.1%
<b>Total</b>		143	100.0%

IHD = ischemic heart disease, CVA = cerebrovascular accident.

**Table 3. Histopathological, biological, and stage findings of study participants**

<b>Parameters</b>		<b>Frequency</b>	<b>%</b>
<b>Biopsy method</b>	Core biopsy	16	11.20%
	Excisional biopsy	127	88.80%
<b>Histological subtype</b>	DCIS	1	0.70%
	Papillary carcinoma in situ	1	0.70%
	IDC, NOS	108	75.50%
	ILC	20	14.00%
	Papillary carcinoma	5	3.50%
	Mucinous carcinoma	3	2.10%
	Paget's disease of nipple	2	1.40%
	Medullary carcinoma	1	0.70%
	Inflammatory breast carcinoma	1	0.70%
	Metaplastic carcinoma	1	0.70%
<b>Tumor size</b>	This	2	1.40%
	T1	39	27.30%
	T2	77	53.80%
	T3	8	5.60%
	T4	10	7.00%
	Unknown	7	4.90%
<b>Lymph node status</b> (M0 at the time of diagnosis)	N0	61	47.70%
	N1	36	28.10%
	N2	16	12.50%
	N3	11	8.60%
	Unknown	4	3.10%

**Table 3. Histopathological, biological, and stage findings of study participants continue.**

<b>Metastasis</b>	M0	124	86.70%
	M1	19	13.30%
<b>Tumor stage</b>	0	2	1.40%
	I	25	17.50%
	II	65	45.50%
	III	29	20.30%
	IV	19	13.30%
	Unknown	4	2.40%
	<b>Tumor laterality</b>	Left	73
Right		65	45.50%
Bilateral		5	3.50%
<b>Tumor focality</b>	Unifocal	118	82.50%
	Multifocal	13	9.10%
	Multicentric	12	8.40%
<b>Lymphovascular invasion</b>	Yes	48	33.60%
	No	78	54.50%
	Uncertain	17	11.90%
<b>ER status</b>	Positive	108	75.50%
	Negative	30	20.90%
	Unknown	5	3.50%
<b>PR status</b>	Positive	98	68.50%
	Negative	40	27.97%
	Unknown	5	3.50%
<b>HER2 status</b>	Positive	23	16.10%
	Negative	115	80.40%
	Unknown	5	3.50%
<b>Histologic grade</b>	Grade I	15	10.50%
	Grade II	77	53.80%
	Grade III	50	35.00%
	Unknown	1	0.70%
<b>Total</b>		143	100%

DCIS=ductal carcinoma in situ, IDC, NOS=invasive ductal carcinoma, not otherwise specified, ILC=invasive lobular carcinoma, ER=estrogen receptor, PR=progesterone receptor, HER2=human epidermal growth factor receptor

**Table 4. Molecular subtypes of study participants.**

<b>Molecular subtype</b>	<b>Frequency</b>	<b>Percentage</b>
Luminal A	61	44.2%
Luminal B	49	35.5%
HER2 over-expression	7	5.1%
Triple-negative	21	15.2%
<b>Total</b>	<b>138</b>	<b>100</b>

**Table 5. Patient pathological, biological, and clinical characteristics of study participants.**

Parameters		Age at diagnosis		Total (N=143)	P value
		≤ 75 years Group 1(N=112) N (%)	> 75 Years Group 2(N=31) N (%)		
<b>Age</b>	Mean age± SD	72.3±3.7	84.9±5.0		
<b>Symptoms at Diagnosis</b>	Asymptomatic	12 (10.7)	0 (0.0)	12	0.047
	Symptomatic	100 (89.3)	31 (100)	131	
<b>Histological subtype</b>	IDC, NOS	81 (72.3)	27 (87.1)	108	0.55
	ILC	18 (16.1)	2 (6.5)	20	
	Others	13 (11.6)	2 (6.5)	15	
<b>Tumor laterality</b>	Right	53 (47.3)	12 (38.7)	65	0.47
	Left	56 (50)	17 (54.8)	73	
	Bilateral	3 (2.7)	2 (6.5)	5	
<b>Tumor focality</b>	Unifocal	89 (79.5)	29 (93.5)	118	0.19
	Multifocal	12 (10.7)	1 (3.2)	13	
	Multicentric	11 (9.8)	1 (3.2)	12	
<b>Lymphovascular invasion</b>	Yes	38 (33.9)	10 (32.3)	48	0.97
	No	61 (54.5)	17 (54.8)	78	
	Uncertain	13 (11.6)	4 (12.9)	17	
<b>Histological grade</b>	I	15 (13.4)	1 (3.2)	16	0.25
	II	59 (52.7)	17 (54.8)	76	
	III	37 (33.0)	13 (41.9)	50	
	Unknown	1 (0.9)	0 (0.0)	1	
<b>ER status</b>	Positive	89 (79.5)	19 (61.3)	108	0.06
	Negative	20 (17.8)	10 (32.3)	30	
	Unknown	3 (2.7)	2 (6.5)	5	
<b>PR status</b>	Positive	83 (74.1)	15 (48.4)	98	0.01
	Negative	26 (23.2)	14 (45.2)	40	
	Unknown	3 (2.7)	2 (6.5)	5	
<b>HER2 status</b>	Positive	19 (17.0)	4 (12.9)	23	0.64
	Negative	90 (80.3)	25 (80.6)	115	
	Unknown	3 (2.7)	2 (6.5)	5	
<b>Molecular subtype</b>	Luminal A	51 (45.5)	10 (32.2)	61	0.07
	Luminal B	40 (35.7)	9 (29.0)	49	
	HER2 positive	6 (5.3)	1 (3.2)	7	
	Triple-negative	12 (10.7)	9 (29.0)	21	
	Unknown	3 (2.7)	2 (6.4)	5	
<b>T category</b>	This	2 (1.8)	0 (0.0)	2	0.21
	T1	30 (26.8)	9 (29.0)	39	
	T2	63 (56.2)	14 (45.2)	77	
	T3	6 (5.3)	2 (6.4)	8	
	T4	5 (4.5)	5 (16.1)	10	
	Unknown	6 (5.3)	1 (3.2)	7	
<b>N category (M0 cases)</b>	N0	50 (47.6)	11(47.8)	61	0.68
	N1	27 (25.7)	9 (39.1)	36	
	N2	14 (13.3)	2 (8.7)	16	
	N3	10 (9.5)	1 (4.3)	11	
	Unknown	4 (3.8)	0 (0.0)	4	
<b>M category</b>	M0	102 (91.1)	22 (71.0)	124	0.004
	M1	10 (8.9)	9 (29.0)	19	

## DISCUSSION

This study focused on the pattern of breast cancer in elderly ( $\geq 65$  years) Kurdish women from a single referral hospital of cancer over seven years. In comparison to the USA, where almost 50% of patients are aged 65 years and older with a median age of 61 years<sup>(13, 14)</sup>, our study revealed a quite different percentage at only 11.3% of female breast cancer patients being 65 years old or older. Our results are more in line with published results from Eastern studies, taking, for instance, two studies from South Korea where the percentages of this age group are 8.9% and 7.2%, respectively<sup>(15, 16)</sup>. Through our study, 91.6% of the older women were symptomatic at the time of presentation; most older women presented with a palpable mass. These values were significantly greater than those discovered in a meta-analysis of breast cancer in older women globally. A meta-analysis revealed that symptomatic presentations happened in 71.8% of the cases<sup>(17)</sup>. The proportion of symptomatic presentation in our study is still higher than that found in a retrospective study in Korea, which was found to be 81.6%<sup>(15)</sup>. The symptomatic presentation tends to be significantly higher in group 2 compared to group 1 in our series ( $p=0.047$ ).

Elderly patients may be diagnosed at an advanced stage because diagnosis may be delayed among the elderly due to a lack of mammographic screening or self-examination. Furthermore, they are less likely to be aware of breast cancer and are more likely to postpone reporting complaints about breast lesions<sup>(18, 19)</sup>.

According to a recent systematic review of studies of ladies over 70 years of age with breast cancer, breast cancer in older women had different clinicopathological characteristics from that in younger patients: breast cancer in the elderly frequently revealed favorable biology (low grade, low lymphovascular invasion, hormone sensitivity, histological types with a good prognosis, lack of HER2 overexpression or amplification, lower Ki67, p53, and EGFR expression), but oddly, a larger tumor size, more lymph node involvement, and more stage IV metastatic disease<sup>(17, 20, 21)</sup>.

The most common histological subtype of breast cancer in our series is infiltrating ductal carcinoma, which is the same pattern we identified in other studies<sup>(22, 23)</sup>. However, other rare histopathologies like papillary carcinoma, mucinous, and medullary were also seen. When compared to a global meta-analysis of breast

cancer in older women, our analysis revealed that invasive lobular carcinoma and papillary carcinoma were more common<sup>(17)</sup>. In addition, invasive lobular carcinoma, papillary carcinoma, and other rare types were more frequent in our study than in Korea<sup>(15)</sup>.

Older women in our study presented with a larger tumor size compared to other studies, and more patients had multifocal and multicentric tumors. Compared to the tumor sizes published in a systematic review, larger tumor size (T3 and T4) was more common in elderly Kurdish women<sup>(17)</sup>. Furthermore, the T1 stage was less common in our study (27.1% in our study vs. 39.1% in a Korean study, 35.3% in a Turkish study), while the T2 stage was more common (53.8% in our study vs. 35.6% in a Korean study, 46.2% in a Turkish study)<sup>(15, 24)</sup>. Our older women had a higher rate of multicentric tumors (8.4% in our study vs. 3.4% in a Korean study)<sup>(15)</sup>. The incidence of multifocal tumors in our study was higher than in the Turkish study (9.1% in our study vs 5.9% in a Turkish study)<sup>(24)</sup>.

Tumor size, histological grading, pathological staging, and lymph node metastasis status are all important prognostic factors in breast cancer. All of them are critical indicators of 5-year survival following the diagnosis. A Swedish Two-County Trial found a persistent association between tumor grade, lymph node status, and tumor size at diagnosis and subsequent survival<sup>(25)</sup>.

Lymphovascular invasion was also more common in our older women than in other studies, occurring in 33.6% of our cases compared to 24.4% of older women in a systematic review<sup>(17)</sup>.

Metastasis to the lymph node was significantly higher in older Kurdish women compared to developed countries (49.2% in our study vs. 39.2% in a meta-analysis, 36% in a Chinese study)<sup>(17, 26)</sup>. While being nearly identical to Jordanian and Turkish studies<sup>(24, 27)</sup>. Moreover, 10.5% of Kurdish older women had distant metastasis at the time of diagnosis. This value was higher than the 6.3% of the meta-analysis<sup>(17)</sup>. However, compared to Jordanian research (20.6%), distant metastasis was less common in Kurdish women<sup>(27)</sup>.

The pathological stage was determined with the clinical staging system of the UICC-pTNM classification. More advanced stages indicate a worse outcome and a lower chance of survival. According to the findings, older Kurdish women were found to be in a more advanced stage than Korean and Chinese studies<sup>(15, 26)</sup>.

The hormone receptor state (estrogen receptor and progesterone receptor) is the best-studied biological characteristic in breast cancer. Estrogen or progesterone receptors, or both, are expressed in approximately 80% of breast tumors and positivity for these receptors is associated with a better prognosis and response to anti-hormonal therapy <sup>(18, 28, 29)</sup>.

Breast cancer biological subtypes, as defined by ER, PR, and HER2 status, have been reported to be age-dependent. ER positivity increases sharply with age, PR positivity increases more slowly, whereas HER2 positivity reduces with age <sup>(30)</sup>.

Compared to published results from the rest of Iraq, Kurdish older women's estrogen and progesterone positivity were higher, while HER2 positivity was lower. Furthermore, luminal A and B levels were more frequent (79.9% vs. 61.1%), while HER2 enrichment was lower in elderly Kurdish women (5.1% vs. 10.7%). The proportion of elderly Kurdish women who were triple negative was slightly higher (15.2% vs. 14.7%) <sup>(31)</sup>.

Estrogen and progesterone positivity was significantly lower in Kurdish older women compared to Jordanian older women. Triple-negative was more common, but HER2 positivity was nearly the same (ER = 75.5% vs 82.8%, PR = 68.5% vs 79.6%, HER2 = 16.1 vs 16.3%, and triple-negative = 15.2% vs 6.9%) <sup>(27)</sup>.

Compared to a meta-analysis, estrogen positivity was significantly lower in older Kurdish women, but progesterone positivity was higher, and HER2 positivity was more common in older Kurdish women <sup>(17)</sup>. Patients with triple-negative breast cancer (TNBC), which lacks an effective treatment target, generally show a poor clinical outcome and are treated with chemotherapy. Treatment of older patients with TNBC should be treated with caution because they usually have a decreased systemic/metabolic function, and the side effects of chemotherapy may be more serious than the clinical outcome of cancer. Appropriate treatment for these patients is needed; however, there are few relevant systematic studies. Recently, the importance of molecular subclassification of TNBC has been emphasized <sup>(32, 33)</sup>.

Breast cancer in the elderly was thought to be relatively indolent, to behave less aggressively, and thus to spread more slowly than in younger individuals <sup>(34)</sup>. Despite this fact, most tumor characteristics were similar between women in the two age groups in our study,

except for progesterone receptor status and metastasis category. Progesterone receptor expression was lower in older patients (74.1% vs. 48.4%, P=0.01). Even estrogen receptor expression was lower in the older group with no reach to significant difference (79.5% vs. 61.3%, P=0.06), and triple negativity was more common in the older group (10.7% vs. 29%, P=0.07). Distant metastasis in older groups was most frequent compared to group 1 (8.9% vs. 29%, P=0.004).

There were several limitations to this study. First, because of its retrospective design, this study had an inherent selection and recall bias. Second, clinicopathological and biological data of elderly breast cancer patients were missing in both our study and previous literature, which could impede accurate comparisons across studies. Third, the study population was too small and was drawn from only one referral center, which does not allow generalization to the entire elderly Kurdish population.

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