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Research Paper

A Comparative Study of Clinicopathological and Immunohistochemistry Features among Sample of Young Patients with Breast Cancer (≤35 years) and Older (> 35 years)

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ABSTRACT:

BACKGROUND:

Breast cancer is the most common malignancy and the leading cause of cancer-related deaths among women worldwide. In Iraq, breast cancer ranks the first among the top ten malignant neoplasm affecting the community. During 2016, 897 women died from the disease, and registered as the first cause of cancer related mortality among Iraqi females (23.6%) and second to bronchogenic cancer (12.1%) among males and females, and this study aimed to evaluate the clinicopathological, immunohistochemistry features of patients with breast cancer ≤ 35 years, in comparison to those > 35 years, and the impact of age on their prognosis.

PATIENTS AND METHODS:

In this retrospective study, medical reports of 220 patients with a known breast cancer, in Baghdad Oncology Teaching Hospital/ Medical City and Babylon oncology center databases were reviewed between February 2017and February 2019. Patients were divided into two groups

RESULTS:

Patients ≤35 years whom had menarche at age ≥ 14 years old were surprisingly higher 19 (17.3%) as compared to patients >35 years 7 (6.4%).according to age, 110 patients aged ≤ 35 years and 110 patients aged > 35 years old.

Most patients at both age group had their first baby within age 20-25 years, while 30 patients (27.3%) ≤ 35 years had their first baby at age 25-29 years old, which was higher than older patients within same age group.

Most of patients presented with grade II disease in both age group ,but 21 (19.1%) of patients ≤35 had grade I disease higher than in >35 years old 1 (0.9%) which was unusual finding as most of younger patients presented with grade III disease. Positive lymph node involvement was found to be higher in 85 patients ≤35 years(77.3%), while it was positive in 61 patients (55.5%) in older than 35 years old.

HER-2 expression was higher in 23 patients (20.9%) who were ≤35 years old, while it was positive in 13 patients (11.8%) older than 35 years.

CONCLUSION:

Breast cancer among young females as proved is quite heterogeneous disease ,and the differences when compared to older females regarding tumor characteristics include clinicopathological, immunohistochemistry features suggest opportunities for further researches to deal with younger age as a distinct group.

KEYWORDS: different age group breast cancer, clinicopathological features, immunohistochemistry features.

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INTRODUCTION:

Breast cancer is the most common malignancy and the leading cause of cancer-related deaths among women worldwide. About 7% of women diagnosed with breast cancer between 2000 and 2005 were below age of 40. [(1)] In Iraq, breast cancer ranks the first among the top ten malignant neoplasm affecting the community; comprising19.5% of total (4996 cases) and 34.3% of female cancers (4922 cases). During 2016, 897 women died from that disease which is the registered as the first cause of cancer related mortality among Iraqi females (23.6%) and the second overall among males and females (12.1%) after bronchogenic cancer.[(2)]

Several studies based on Iraqi National Breast Cancer Research Program in collaboration with the International Agency for Research on Cancer/WHO have documented that Iraqi females often present with breast cancer at younger ages, advanced stages and with more aggressive behavior than their Western counterparts.

Interestingly, breast cancer risk factors, clinical outcomes, and tumor biology are somewhat different in the subgroup of women below 40, suggesting that breast cancer in young women represents a distinct entity. [3]

There are still controversies about the definition of "very young age". International multicenter clinical trials considered 35 years as the age boundary (Lilla Madaras et al., 2013). [5]

Tumors in women younger than 35 are more likely to be of a higher histological grade[3], and to be classified as estrogen receptor (ER) and progesterone receptor (PR) negative, and increase proportion of ER/PR negative with human epidermal growth factor receptor 2 (HER-2) over expression, Also have high proliferation index and lymphovascular invasion.[6]

These breast cancer patients have to deal with many issues related to fertility, self-image, psychosocial distress and professional integration.

Breast cancer in a woman under age 35 years should prompt one to consider familial breast cancer syndromes and genetic testing for *BRCA1/2* mutations and, less commonly, *TP53* mutations. In a population-based case control study, the likelihood that a woman with breast cancer under the age of 35 had a detectable *BRCA1/2*mutation was 9.4% (compared to a population prevalence of 0.2%); these findings have been demonstrated by other studies as well.[3]

Tumor characteristics can help identify women who are likely to carry a *BRCA1* mutation. High grade triple negative breast cancers are more common in women with *BRCA1* mutations, whereas pathologic and immunohistochemical features of tumors associated with *BRCA2* mutations are similar to those of sporadic cases [3]. Women who test positive for a *BRCA1/2* mutation have a 40 to 50% chance of developing a second primary breast cancer, also at increased risk for ovarian cancer, with a lifetime risk of 40 to 50% in *BRCA1* carriers and 10 to 20% in *BRCA2* carriers.[3]

There is an age effect of risk reduction bilateral salpingo-oopherectomy (RRBSO) on breast cancer risk; women after age 50 do not obtain a significant reduction in the risk of breast cancer. RRBSO does not seem to affect the risk of contralateral breast cancer after a prior diagnosis of breast cancer; there is a significant reduction in mortality in woman with ER-negative breast cancer who have a BRCA 1 mutation (HR 0.38 ; P=0.007).[8]

Bilateral risk-reduction mastectomy (RRM) has been shown to reduce the risk of breast cancer by more than 90% in women with hereditary breast and ovarian cancer syndromes.[9]

Women who achieve chemotherapy-induced amenorrhea have a better prognosis than women who retain their menses.[10]

Overall survival was significantly improved in women who achieved at least 6 months of chemotherapy-induced amenorrhea, regardless of chemotherapy, and surprisingly, regardless of hormone receptor status.[10]

With young premenopausal women (<35 years) less likely to achieve amenorrhea with chemotherapy compared with older premenopausal women.[11]

Pregnancy after a diagnosis of early stage breast cancer does not appear to increase the risk of relapse or decrease survival.[12]

AIM OF THE STUDY:

To evaluate the clinic pathological, immunohistochemistry features of breast cancer in young Iraqi female less than 35 years in comparison to those older than 35 years, and the impact of age on prognosis in younger patients.

MATERIAL AND METHOD:

This research is a retrospective study of the data extracted from the information system database of Baghdad Oncology Teaching Hospital, Medical city and Babylon oncology center, Babil during February 2017- February 2019.

220 patients were included in this study with a known breast cancer proved by histopathological reports. Patients were divided into two groups according to age , 1st group, 110 patient were less than 35 years and 2nd group, 110 patient were more than 35 years old.

Patients that had been excluded from this study were patients with two different malignancies. Overall 220 patients were enrolled in this study. The evaluated variables included age, weight, height, age at menarche, marital status, age of 1st baby, Staging, grading, lymph vascular invasion and histological subtype taken from histopathological reports.

Estrogen receptor ER , progesterone receptor PR and HER-2 status was evaluated with immunochemistry and +3 was defined as positive, those with +2 were further evaluated by FISH or CISH study.

Data confidentiality and ethical approval

1.The study protocol was approved by the scientific Iraqi council of medical oncology.

2.Agreement and permission of the director of the center was obtained.

3.Data of the patients were kept confidentially and not disclosed to unauthorized persons.

4.Any data or information that leads to identification of the participant were hided and replaced with specific serial codes.

Statistical analysis

Data was analyzed using statistical package for the social sciences (SPSS version 23) computer software program.

Descriptive statistics presented as frequency tables, Continuous variables were expressed as mean ± standard deviation and categorical variables as numbers and percentages. Analytic statistics as chi-square test to find association between two categorical variables. The P-value below or equal to 0.05was considered to be statistically significant.

RESULTS:

A total of 220 breast cancer patients were enrolled in this study, 110 patients were ≤35 years and 110 patients > 35 years. The mean age if patients ≤35 years was 31.5(±3.3) of those patients 23.6% (26) patients were below 30 years and 76.4% (84) of patients were between 30-35 years, figure 11.

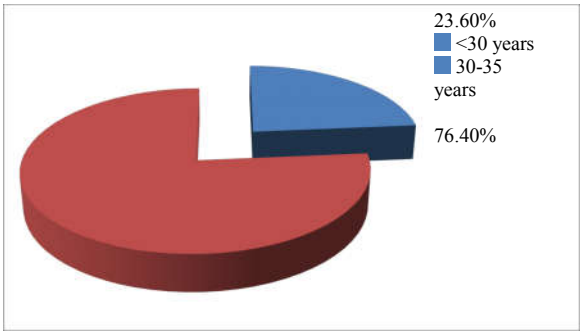


Figure 1 :Age Distribution among patients ≤35 years.

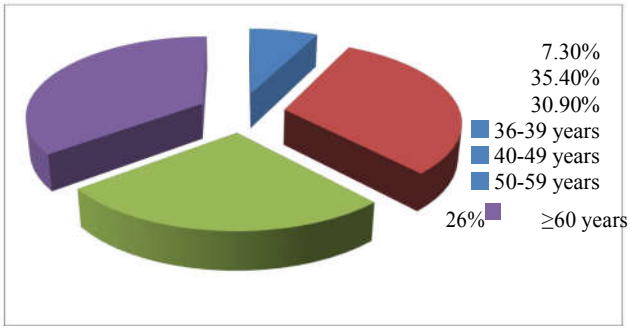


Figure 2: Age distribution among patients >35 years.

Age of menarche had a significant association between two groups of breast cancer patients (p value =0.003) where 3.6% of patients ≤35 years had menarche at age of ≤ 11 years, 17.3% of them had menarche at age of ≥ 14 years while 13.6% of patients >35 years had menarche at age ≤11 years, 6.4% at age of ≥14 years. Majority of patients had menarche between 13-14 years in both groups.

Table 1: Relation of patient characters between two age group.

Variable		Breast cancer patients Age		Total	P value
		≤35 years	>35 years		
Marital status	Married	96 (87.3%)	103(93.6%)	199(90.5%)	0.108*NS
	Unmarried	14(12.7%)	7(6.4%)	21(9.5%)	
Age of menarche	≤11 years	4(3.6%)	15(13.6%)	19(8.6%)	0.003*S
	12-13 years	87(79.1%)	88(80%)	175(79.5%)	
	≥ 14 years	19(8.6%)	7(6.4%)	26(11.8%)	
Age at first baby	Nulliparous	14(12.7%)	10(9.1%)	24(10.9%)	0.017*S
	<20 years	8(7.3%)	18(16.4%)	26(11.8%)	
	20-24 years	57(51.8%)	67(60.9%)	124(56.4%)	
	25-29 years	30(27.3%)	14(12.7%)	44(20.%)	
	≥30 years	1(0.9%)	1(0.9%)	2(0.9%)	
BMI in kg/m2	Normal (18.- 24.9) & Underweight (<18.5)	39(35.5%)	37(33.6%)	76(34.5%)	0.95* NS
	Overweight (25-29.9)	40(36.4%)	42(38.2%)	82(37.3%)	
	Obese (≥30)	31(28.2%)	31(32.3%)	62(28.2%)	
Total		110(100%)	110(100%)	220(100%)	

Regarding grade of tumor, 19.1% of patients ≤35 years had grade I disease, 58.2% of patients had grade II and 22.7% of patients had grade III, while in patients >35 years only one patient had grade I cancer, 65.5% of patients had grade II and 33.6% of patients had grade III cancer with a significant P value (p=0.001).

Only 9.1%(10) of patients≤35 years and 8.2%(9) of patients >35 years were diagnosed at stage I, while 22.7%(25) of patients≤35 years and 20%(22) of patients >35 years were diagnosed at stage IV and there were no significant association between stage of cancer and age (P=0.25).

Positive lymph node at presentation was foundin 77.3% of patients≤35 years and 55.5% of patients >35 years. Negative lymph node was found in 22.7% of patients ≤35 years and 44.5% of patients >35 years with significant P value (p=0.001).

The distant metastasis was found in 22.7% of patients≤35 years and 20% of patients >35 years with no significant P value (P=0.62), table 3-2.

Table 2: Relation of stage and grade of cancer with two age groups

Variables		Breast cancer patients Age		Total	P value
		≤35 years	>35 years		
Grade of Cancer	I	21 (19.1%)	1 (0.9%)	22(10%)	0.0001* S
	II	64 (58.2%)	72(65.5%)	136(61.8%)	
	III	25(22.7%)	37(33.6%)	62(28.2%)	
Stage of cancer	I	10(9.1%)	9(8.2%)	19(8.6%)	0.25* NS
	II	33(30%)	47(42.7%)	80(36.4%)	
	III	42(38.2%)	32(29.1%)	74(33.6%)	
	IV	25(22.7%)	22(20%)	47(21.4%)	
Primary tumor diameter	T1	22(20%)	14(12.7%)	36(16.4%)	0.38* NS
	T2	58(52.7%)	62(56.4%)	120(54.5%)	
	T3	25(22.7%)	25(22.7%)	50(22.7%)	
	T4	5(4.5%)	9(8.2%)	14(6.4%)	
Regional lymph node	Negative	25(22.7%)	49(44.5%)	74(33.6%)	0.001*S
	Positive	85(77.3%)	61(55.5%)	146(66.4%)	
Distant metastasis	Negative	85(77.3%)	88(80%)	173(78.6%)	0.62*NS
	Positive	25(22.7%)	22(20%)	47(21.4%)	
Total		110(100%)	110(100%)	220(100%)	

Chi-square test, NS= non-significant significant .

For the patients ≤35 years, 43.3% of patients had PR,ER +ve& HER2 –ve, 20% of patients was triple positive, 15.4% of patients had triple negative and 20.9% of patients had Hormonal –ve& HER2 +ve while for patients > 35 years 63.6%(70) of patients had PR,ER +ve& HER2 –ve, 13.3% of patients had Triple positive, 10.9% of patients had triple negative and 11.8% of patients had Hormonal –ve& HER2 +ve with significant P value (p=0.02).Lymphovascular invasion (LVI) was positive in 55.5% of patients ≤35 years and 51.8% of patients >35 years with no significant association P value (p=0.58), table 3-3.

Table 3: Relation of hormonal status and LVI with age groups.

Variables		Breast cancer patients Age		Total	P value
		≤35 years	≤35 years		
Hormonal status	PR,ER +ve& HER2 –ve	48 (43.3%)	70(63.6)	118(53.6%)	0.02*S
	Triple Positive	22 (20%)	15(13.3%)	37(16.8%)	
	Triple Negative	17(15.4%)	12(10.9%)	29(13.1%)	
	PR,ER –ve& HER2 +ve	23(20.9%)	13(11.8%)	36(16.3%)	
Lymph vascular Invasion	Positive	61(55.5%)	57(51.8%)	105(47.7%)	0.58* NS
	Negative	49(44.5%)	53(48.2%)	115(52.3%)	
Total		110(100%)	110(100%)	220(100%)	

Chi-square test . NS= non-significant, S significant .

Invasive ductal carcinoma was found in 90.9% of patients ≤35 and patients >35 years, 1.8% of patients ≤35 years and 5.5% of patients >35 years had ILC, figure 3.

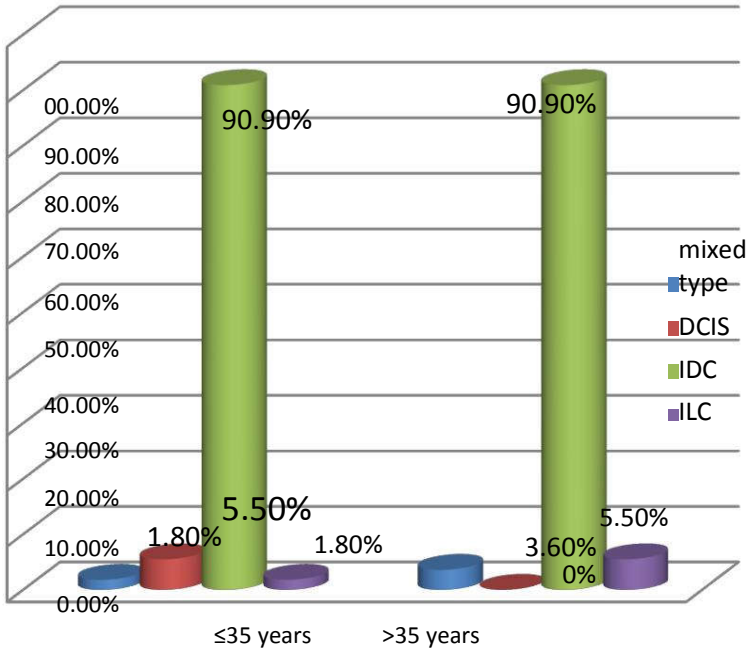
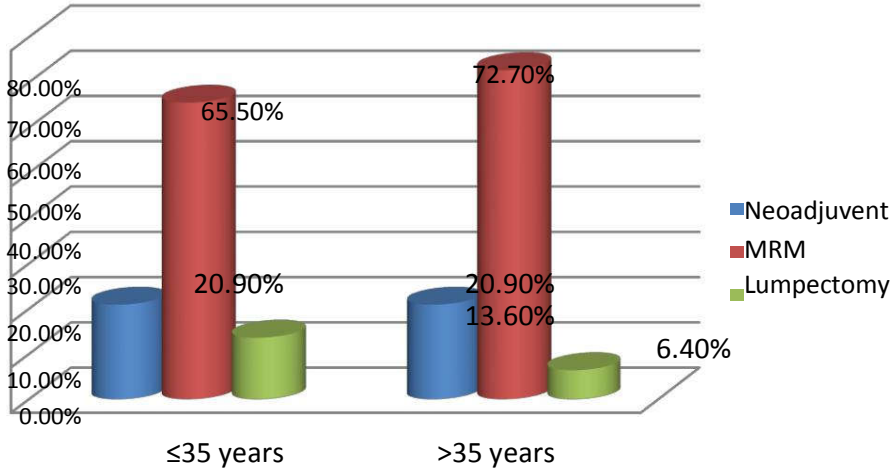


Figure 3: Bar chart for histopathological type of cancer in two age groups.

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

20.9% of patients in both age group had received neoadjuvant chemotherapy, while mastectomy was performed in 65.5% of patients ≤35 years and in 72.7% of patients > 35 years. Lumpectomy was done for 13.6% of patients ≤35 years and 6.4% of patients >35 years, figure 3-4.



MRM, modified radical mastectomy

Figure 4: Bar chart for type of surgery in two age groups.

DISCUSSION:

Although the occurrence of Breast cancer in young women (BCYW) is considered a rare disease, various studies were done in the subject, and they have shown that the disease has an aggressive course in young patient with a poor disease outcome. Unfortunately, till the moment, breast cancer is the most commonly diagnosed cancer among young women in Iraq.[13]

The mean age for patients less than 35 years old (110 patients) was 31.5, 26 patients (23.6%) were less than 30 years old, and 76.4% (84 patients) were between 30-35 years, as the incidence of breast cancer became less in twenties, and most of younger age group with breast cancer were between 30-35 in this study (figure 2).

Most of patients had their menarche at age between 12-13 years in both age groups (P value 0.003) (table 1). 4 patients (3.6%) ≤ 35 years old had menarche at age of less than 11 years old while > 35 years was 15 patients (13.6%).

19 patients (17.3%) ≤ 35 years were ≥14 years old for menarche, which is higher than older patients (7 patients) 6.4% within same age group, which is inconsistent with Khalel EA study that show 57 from total 73 (78.1%) of patients were less than12 years old at group age less than 40 years old, early age of menarche less than 10 years old is an established risk factor for development of breast cancer with relative risk 1.4 – 1.9.[13]

There was a significant association between the two age groups regarding the age of giving birth to the first baby, as the majority of both groups had their first baby at age (20-24) years old, 57 patients (51.8%) and 67 patients (60.9%) respectively; patients ≤35 years old and within age group 25-29 years old seem to had higher percentage 30 patients (27.3%) while >35 years old was 14 patients (12.7%) (table 1), which is similar to Khalel EA study which showed majority of first baby at age less than 30 years (80.8%).[13].

Rodriquez et.al. found that women less than 35 years, early childbearing and multiparity are risk factors, due to short term rise (several months immediately following birth) in breast cancer risk. [14]

Most patients had Grade II in both age group (58.2% for ≤35 years, 65.5% for ≥ 35 years (table 2); however, there was a statistically significant (p value0.023) regarding grade I, patients < 35 years old

19.1% while > 35 years old was (1) 0.9%, which was unusual presentation for younger age whom

usually presented with grade III and being more aggressive behavior and this is inconsistent with Bakkach J. et al study which show higher percent of grade III 40.2% in younger than 35 years old.[7]

There is a significant association (p value 0.001) (table 3-2) between the two age groups and regional lymph node involvement, patients < 35 years old presented with lymph node involvement 77.3%, versus 55.5% for >35 years old; which resembles the results published by Zeeshan S. etal that also showed higher percentage of patients < 40 years old presented with positive lymph node 70.9% (256 from total 366). [4]That's may relate to a well-established fact of a more aggressive behavior of disease in the younger age group with more lymph node involvement at presentation.

Immunohistochemistry study of the tumors was significantly different between two age group P value 0.02 (table 33), in which ER/PR negative HER2 positive in ≤35 years were 20.9% , 11.8% for >35 years old. ER,PR positive, HER-2 negative still higher in both age groups, which is inconsistent with Bakkach J. et al study that showed higher percentage of TNBC 23% younger than 35 years, while HER-2 positive percentage was 10.8% of the same age group.[7]WeiXQ et al study showed similar percentage between all molecular classification, luminal A 23.7%, luminal B 27.1%, HER-2 positive 22%, triple negative 27.1% (from total of 118 less than 35 years) [5], that's may be explained by different biological behavior of disease.

Invasive ductal carcinoma was found in (100) 90.9% patients ≤ 35years (figure 3), same percent for older than 35 years, which is similar to Wei XQ et al study that showed predominant invasive ductal carcinoma in 83.9%(99 from total 118) in younger than 35 years, and 83.9% (1158 from total 1380) older than 35 years.[5]

Patients whom started neoadjuvant chemotherapy were 20.9% in both ≤35 and >35 years old (figure 3-4), while lumpectomy was done in (13.6% patients ≤35 years, and 6.4% patients >35 years, which is similar to Wei XQ et al study that showed lumpectomy done in 12.7% (20 from total 118).[5]while in Kataoka A.

et al study showed that lumpectomy done in 62.7%(1844 from total of 2982) patients less than 35 years, and 57%(59822 from total 106295) older than 35 years.[15] that's may relate to that a larger number of patients presented with early stage that made patients very suitable for breast conserving surgery.

CONCLUSION:

As a comparison to patients older than 35 years, young age breast cancer less than 35 years old whom involve into this retrospective study are characterized with:

1. Patients ≤ 35 years old had menarche mostly at age between 12-13 years so as > 35 years, with higher number of patients with late menarche at ≥14 years in patients ≤35 years old.
2. Majority of patients in both age groups had their first baby at age of (20-24) years old. patients ≤ 35 years old and within age group between 25-29 years old seems to had higher number of patients having their first baby at this age group.
3. Grade I was found to be higher in ≤ 35 years as compared to older patients, which was unexpected as most of younger age patients usually presented with more aggressive behavior and being grade III disease.
4. Regional lymph node was found to be positive in most of patients ≤ 35 years.
5. HER-2 expression was found to be positive more in ≤ 35 years old as compared to older patients.
6. Also this study found that in term of treatment choices, our patients underwent radical mastectomy rather than conserving surgery, which adds further challenge for these young women at the emotional and psychosocial levels, especially in the absence of a specialized psychological support.

Recommendation

1. There is still a considerable proportion of breast cancer patients in Iraq presented with locally advanced disease at the time of diagnosis, which justifies the necessity to promote public awareness educational campaigns to strengthen our national early detection program.
2. Improve surgical options regarding young female and impact of more aggressive local surgical treatment on her psychosocial life, this includes a multiple options for breast conserving surgery and breast reconstruction surgery following mastectomy (immediate or delayed), breast implant (tissue expander placement or autologous tissue transplantation involved fat grafting, various microsurgical flaps from abdomen, back and thighs).
3. Further studies are needed including larger sample size and multi centric contributions to demonstrate the impact of age on prognosis in younger age female with breast cancer.

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