Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 8, Nov. 2024
Manuscript ID ZUMJ-2408-3524 DOI . 10.21608/zumj.2024.313346.3524
ORIGINAL ARTICLE

Impact of Low HER2 Expression on Neoadjuvant Treatment Response in Early Luminal Breast Cancer

Amrallah A. Mohamed[1], Ola M. Elfaragy[1], Fatma Mohamed Erfan Abdelwahab*[1], Aziza E.Abdelrahman[2]

[1]Medical Oncology Department, Faculty of Medicine, Zagazig, Egypt
[2]Pathology Department, Banha Teaching Hospital, Al-Qalyubia, Egypt

Corresponding author*:
Fatma Mohamed Erfan Abdelwahab

Email:
fatmaerfan26@gmail.com

Submit Date 20-08-2024
Accept Date 05-09-2024

ABSTRACT

Background: Human epidermal growth factor receptor 2 **(**HER2) is a significant driver gene among breast cancer (BC) and a gene locus for anti-HER2 targeted therapy. Amplification of the HER2 gene often indicates poor prognosis. We aimed to evaluate the impact of low HER2 expression in response to neoadjuvant chemotherapy (NAC) and survival outcomes in early luminal BC.**Methods:**We conducted this retrospective cohort study on 100 female patients with early luminal BC with low HER2 expression treated using NAC. The primary endpoint was to evaluate the pathological response, secondary endpoint was to evaluate clinicopathological criteria, disease-free survival (DFS) as well as overall survival (OS).**Results:** Invasive ductal carcinoma (IDC) was the commonest pathological type (76.0%), and Grade II was the commonest (73.0). T2 was the commonest (78.0%). N2 was the commonest (39.0%), stage II was the commonest (48%), 5-years DFS was (79.7%) with average (30.0±25.52) months while 5-years OS rate was (79%) with the average (38.82±27.54) months, 16% had pathological complete response (pCR) and 84% hadn't pCR with statistically significant difference in distribution. A statistically significant relation was revealed between the pCR and pathological type (P value= <0.002), pCR was significantly associated with 5 years of DFS (P <0.001) and OS (P <0.001).**Conclusions**: Our results did not show a significant impact of low HER2 on pCR, DFS, or OS, but showed low pCR achievement especially as most were HR-positive. Low HER2 may be a distinct biological entity that requires further research with a prospective nature and adequate population. With the new HER2 targeting ADCs which prove beneficial in low HER-2 patients' preparatory activity data, patients with low HER2 may considered a special population subset for finding new treatment options to NAC to

improve BC results.

Keywords: Low HER2 Expression, Neoadjuvant Treatment Response, Early Luminal BC.

INTRODUCTION

Breast cancer is the most common malignancy among women with estimated new cases globally of 1,384,155 and nearly 459,000 related deaths [1]. More than 22,000 new cases of breast cancer are detected each year in Egypt, making it the most common malignancy in women. This is anticipated to experience a meteoric ascent in the next years due to factors such as a growing population, shifting demographic dynamics, and the increasing adoption of Western lifestyle practices [2].

Ductal carcinoma in situ (DCIS), stages I, IIA, IIB, and IIIA BC, as well as those that have not spread outside the breast or axillary lymph nodes are referred to as early-stage BC. More than 80% of patients have achieved long-term survival following surgery, whether or not they received adjuvant treatment. [3].

Among the several molecular subtypes of BC, almost 75% are luminal BC, which are classified as BC and are positive for ER and/or PR. One type is luminal A, while the other is luminal B[4].

The Luminal A BC subtype is characterized by positive ER and PR, low Ki-67 expression level, and HER2-negative status. Contrarily, Luminal B has ER-positive and /or PR-positive, HER2-negative, and has high levels of Ki-67[4]. Or characterized by HER2 positivity and the presence of ER and/or PR [5].

HER2 Positive BC is defined as BC that shows evidence of gene amplification via immunohistochemistry (IHC) +3 or fluorescence in situ hybridization (FISH). All other tumors have been labeled as Her-2-negative BCs [6]. IHC score 1+ or 2+ and a negative ISH referred to low HER2 expression in BC. [7].Lacking ER, PR, or HER2 proteins by IHC is classified as triple-negative BC [8].

Historically, NAC was employed to accomplish surgical resection in cases of locally advanced, unresectable BC. To make breast-conserving surgery (BCS) more feasible, it was subsequently expanded to resectable cases with the goal of tumor downsizing [7].

Therefore, the current study aimed to evaluate the impact of low HER2 expression in response to neoadjuvant chemotherapy (NAC) as well as survival outcomes in early luminal BC.

METHODS

This observational retrospective cohort study was conducted on 100 female patients who had early luminal BC with low HER2 expression treated using NAC at the Department of Medical Oncology, Faculty of Medicine, Zagazig University. All patients were non-metastatic at the time of the presentation and received NAC followed by surgery with cure intent.

Sample size: The comprehensive sample was collected from all the cases that were diagnosed, treated, and followed up at the Medical Oncology Department at Zagazig University in the period from January 2015 until December 2022 and met the inclusion criteria. Human subjects research adhered to

the Helsinki Declaration, a code of ethics established by the World Medical Association. The Institutional Review Board (IRB#101054) gave its approval before this study could begin. The confidentiality and personal privacy of all participants were upheld throughout the study. The data that was acquired was not utilized for any other purpose.

Cases with the following criteria were included: female patientsaged ≥ 18 years old years, who had pathologically proven diagnosis of BC, with clinical stage I-III, ER, and /or PR positive and low HER2, and patients who received NAC before curative surgery with curative intent. Cases with the following criteria were excluded: male patients, patients with recurrent or metastatic BC, patients who had undergone curative surgery before taking any lines of chemotherapy, as well as patients with HER2 +ve BC. IHC and ISH results, IHC 0 was classified as HER2-negative, IHC 1+ or IHC 2+/ISH- were considered HER2-low, and IHC 2+/ISH+ or IHC 3+ was classified as HER2-positive [16].

Methods:

Data collection:

The following data were anonymously extracted from patients' medical files from the Medical Oncology Department and transcribed into an Excel spreadsheet:

Personal data including age & residence, date of diagnosis with BC, detailed history and full physical examination at the time of the diagnosis and every follow-up visit, family history of BC, and menopausal status at the time of the diagnosis. In addition, clinical examination and clinical staging at diagnosis included TNM staging. Documentation of the type of surgery had been done which was either modified radical mastectomy (MRM) or BCS.

Pathological data were documented from the department of pathology including pathological subtype, histological grade, tumor size, lymph node status, and a number of the positive lymph nodes for metastasis, TNM, and pathological staging were done using the American Joint Committee on Cancer (AJCC) Staging system [9] and IHC assessment ER, PR, HER2, KI67. Results were recorded in the data sheet after the assessment of expression by IHC using paraffin-embedded blocks in the Pathology department, at Zagazig University hospitals.

The full data about NAC received by the patient were reported including the type of chemotherapy received (i.e. NAC regimen used in the treatment) and, the number of cycles of chemotherapy received.

The pathological response post NAC was reviewed from patient files. Surveillance/Follow-up data after the end of treatment were documented including data about local or contralateral recurrence if occurred during the follow-up period of the patients (if present, date of recurrence data was documented). In addition, data about distant metastasis occurred during surveillance/follow-up of the patients (if present, the date was documented) and lastly patient's last visit date or the date of death and current condition of the patient on the last visit during surveillance/follow up.

Assessment of pathological response: pathological complete response (pCR) was defined as the absence of invasive carcinoma in the breast as well as in the axillary lymph nodes at the time of surgery [10].

Assessment of survival outcome (OS&DFS):

Using the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) as the standard, DFS was defined as the duration from the last therapy (surgery) till the occurrence of any local or distant recurrence. OS was defined as the interval between diagnosis to death, regardless of the cause of death [11].

Endpoints

The primary endpoint was to evaluate the pathological response, secondary endpoint was to evaluate the clinicopathological criteria of our study group, DFS, and OS.

Statistical Analysis:

Data were checked, entered, and analyzed using SPSS version 23 for data processing. Quantitative variables used mean and standard deviation; qualitative variables were presented as numbers and percentages. Chi-square test (X2): Used to find the association between row and column variables correlation. Fischer exact test is used instead of the chi-square test if one cell is less than 5, Regression analysis; used for the prediction of the predictor factors of survival (DFS& OS) using Kaplan-Meier method, P<0.05 was considered significant.

RESULTS

The mean age of the studied group was (48.5±8.6) ranging from (32 to 53) years, about two-thirds of them (61.0%) were rural residents, about half of them were postmenopausal and all of them were married (100.0%). Regarding the clinical data, the mean BMI of the studied group was (34.3±4.9) ranging from 28.5 to 46.0, and more than half of them (64.0%) had |PS 0, Most of them (95.0%) didn't have a family history of BC and (72.0%) didn't have comorbidities (Table 1).

Table (2) showed that IDC was the commonest pathological type (76.0%). Grade II was the commonest (73.0). All the studied groups (100.0%) were ER-positive, (85.0%) were PR positive, and (56.0%) were Ki67 low. Regarding tumor size, T2 was the commonest (78.0%) followed by T1(10.0%). Lymph node (LN) involvement, N2 was the commonest (39.0%). Most of our population were stage II, and III presented by 48% and 46.0% respectively. Most of the studied group (89.0%) had MRM and (11.0%) did BCS. Adriamycime Cyclophosphamide protocol (AC)(4cycles) every 3 weeks followed by 12 weeks of Taxol was the commonest chemotherapy (62.0%) followed by AC 4 cycles (27.0%) then Taxotere cyclophosphamide protocol (TC)(4 Cycles) every 3 weeks and TC 4 cycles every 3 weeks only (8.0%) for each and lastly AC 4 cycles& DD Taxol 4 cycles every 2 weeks with growth factor support (3.0%). Regarding pathological response, 16% of the studied population were in complete pathological response and 84 patients still had residues (84%) with statistically significant differences in distribution.

Statistically significant relations were revealed between the pathological response and pathological type (p <0.001) (Table 3).

According to survival, LN staging, pathological response was significantly associated with 5 years DFS (p= <0.001, and <0.001 respectively). Also, tumor size, LN staging, and pathological response were found to have a significant impact on 5 years OS (p= 0.045, <0.05, <0.001 respectively) (Table 4).

Multivariate COX regression analysis shows that comorbid hypertension, and high Ki67,

significantly independently increased the hazard ratio affecting OS by 11.99 and 2.3 folds respectively. diabetes, non-significantly independently increase hazard ratio by 2.1 folds. PS 2 significantly independently decreases the hazard ratio. PS 1, comorbid hypertension significantly independently increased the hazard ratio affecting DFS by 93.69 and 42.84 folds respectively (Table 5).

Concerning survival rate and time, the 5-year DFS rate among the studied group was (79.7%) with an average (of 30.0±25.52) months ranging from (8 to 96) months while the 5-year OS rate was (79%) among the studied group with an average (of 38.82±27.54) months ranging from (12 to 108) months (Table 6 and Figure 1)

Table (1) Socio-demographic data and history of the studied group:

Demographic data		**The studied group (n=100)**
		N(%)
Age (years)	Mean ± SD	48.5±8.6
	Median	49
	Range	(32-53)
BMI	Mean ± SD	34.3±4.9
	Median	32.5
	Range	(28.5-46.0)
Residence	Rural	61 (61.0%)
	Urban	39 (39.0%)
Menopausal	Premenopausal/perimenopausal	49 (49.0%)
	Postmenopausal	51 (51.0%)
Marital status	Married	100 (100.0%)
Performance status	0	64 (64.0%)
	1	32 (32.0%)
	2	4 (4.0%)
Family history of BC	No	95 (95.0%)
	Yes	5 (5.0%)
Comorbidities	Absent	72 (72.0%)
	HTN	8 (8.0%)
	D.M	8 (8.0%)
	HTN & D.M	12 (12.0%)

BMI= Body Mass Index, HTN= hypertension , D.M = diabetes mellitus

Table (2) Pathological features, treatment, andpathological complete response among the studied group:

Pathology and markers		The studied group (n=100)
		No(%)
Pathology	IDC	96 (96.0%)
	ILC	4 (4.0%)
Grading	G 1	0 (o%)
	G II	73 (73.0%)
	G III	27 (27.0%)
ER	Negative	0 (0.0%)
	Positive	100 (100.0%)
PR	Negative	15 (15.0%)
	Positive	85 (85.0%)
IHC+1	1	78 (78.0%)
IHC+2/SISH-	2	22 (22.0%)
Ki67	Low (<20%)	56 (56.0%)
	High (>20%)	44 (44.0%)
Tumor size (cT)	TI	10 (10.0%)
	T2	78 (78.0%)
	T3	4 (4.0%)
	T4	8 (8.0%)
Lymph node staging(cN)	N0	33 (33.0%)
	N1	16 (16.0%)
	N2	39 (39.0%)
	N3	12 (12.0%)
Stage	I	6 (6.0%)
	II	48 (48.0%)
	III	46 (46.0%)
Type of surgery	MRM	89 (89.0%)
	BCS	11 (11.0%)
Neoadjuvant chemotherapy regimen	AC& weekly Taxol	62 (62.0%)
	AC(4 cycles)	27 (27.0%)
	TC (4 Cycles)	8 (8.0%)
	AC& DD Taxol	3 (3.0%)

		The studied group (n=100)	P value
		N(%)	
pCR	Yes	16 (16%)	<0.001**
	No	84 (84%)	

IDC=invasive ductal carcinoma, ILC=invasive lobular carcinoma, ER=estrogen receptor , PR=progesterone receptor , HER2=human epidermal receptor , IHC=immunohistochemestry , MRM =modified radical mastectomy ,BCS =breast conservative surgery , AC =adriamycime cyclophosphamide protocol , TC=taxotere cyclophosphamide protocol ,DD=dose dense, pCR(pathological complete response)

Table (3) Univariate analysis for the predictor factors affecting pathological remission among studied group:

Variables	Non pCR n=84 (%)	pCR N=16(%)	χ^2	p-value	Odds ratio 95% CI.
Residence					
Rural (no=61)	47 (77%)	14 (23%)	5.623	0.018*	
Urban (no=39)	37 (94.9%)	2 (6.1%)			5.51 (1.18-25.8)
Menopausal					
Premenopausal (no=49)	39 (79.6%)	10 (21.4%)	1.389	0.239	
Postmenopausal (no=51)	45 (88.2%)	6 (11.6%)			1.92(0.54-5.8)
Performance status					
0 (no=64)	48 (75%)	16 (25%)	9.429¥	0.002*	1 (reference)
I (no=32)	32 (100%)	0 (0%)			∞
II (no=4)	4 (100%)	0 (0%)			∞
Comorbidity					
No (no=28)	28 (100%)	0 (0%)	7.407	0.006*	
Yes (no=72)	56 (77.8%)	16 (22.2%)			∞
Pathology					
IDC (no=96)	84 (87.5%)	12 (12.5%)	FET	**<0.001 ****	∞
ILC(no=4)	0 (0%)	8 (100%)			
PR					
Negative (no=15)	15 (100%)	0 (0%)	FET	0.12	∞
Positive (no=85)	69 (81.2%)	16 (18.8%)			
HER2					
HER2-1 (no=78)	66 (84.6%)	12 (15.4%)	FET	0.748	1.22(0.35 – 4.24)
HER2-2 (no=22)	18 (81.8%)	4 (18.2%)			
Ki67					
Low (no=56)	44 (78.6%)	12 (21.4%)	2.791	0.095	
High(no=44)	40 (90.9%)	4 (9.1%)			2.72 (0.81-9.15)
Tumor size					
TI (no=12)	8 (66.7%)	4 (33.3%)	3.465¥	0.063	1 (reference)
T2 (no=76)	70 (92.1%)	6 (7.8%)			5.83 (1.35-25.2)
T3(no=4)	2 (50%)	2 (50%)			0.5(0.05-4.98)
T4 (no=8)	4 (50%)	4 (50%)			0.5 (0.08-3.13)
Lymph node staging					
N0(no=33)	31 (93.9%)	2 (6.1%)	1.794¥	0.181	1 (reference)
NI (no=16)	14 (87.5%)	2 (12.5%)			0.45 (0.06-0.44)
N2 (no=39)	27 (69.2%)	12 (30.8%)			0.15 (0.03-0.71) ∞
N3(no=12)	12 (100%)	0 (0%)			
Stage					
I (no=6)	1 (16.7%)	5 (83.3%)	2.365¥	0.124	1 (reference)
II (no=48)	45 (41.6%)	3 (58.4%)			75 (6.5-864.4)
III (no=46)	38 (4.5%)	8 (95.5%)			23.75 (2.4-231.8)
Surgery					
MRM(no=89)	75 (84.3%)	14 (15.7%)	FET	>0.999	0.3
BCS(no=11)	9 (81.8%)	2 (18.2%)			(0.09-1.2)
Chemotherapy					
AC &Taxol (no=62)	52 (83.9%)	10 (16.1%)	2.874	0.579	1 (reference)
AC (no=27)	21 (77.8%)	6 (22.2%)			0.67 (0.22 - 2.1)
TC (4 Cycles) (no=8)	8 (100%)	0 (0%)			∞
AC & DD Taxol (no=3)	3 (100%)	0 (0%)			∞

IDC=invasive ductal carcinoma, ILC=invasive lobular carcinoma, ER=estrogen receptor, PR=progesterone receptor, HER2=human epidermal receptor, IHC=immunohistochemestry, MRM =modified radical mastectomy,BCS =breast conservative surgery, AC =adriamycime cyclophosphamide protocol, TC=taxotere cyclophosphamide protocol,DD=dose dense* Statistically significant.** Statistically highly significant.FET=Fisher Exact test χ^2Chi-square test §Chi square for trend test

Table (4) Univariate analysis for the predictor factors affecting the disease-free survival, and overall survival among studied group:

Disease Free survival		
Variables	CHR (95% CI)	**p-value**
Residence		
Rural	1 (reference)	0.463
Urban	1.22(0.72 – 2.06)	
Menopausal		
Premenopausal	1 (reference)	0.034*
Postmenopausal	1.82(1.05 – 3.16)	
Performance status		
0	1(reference)	<0.001**
I	3.3(1.66 – 5.53)	
Comorbidity		
No	1(reference)	0.01*
Diabetes	1.58(0.7 – 3.55)	0.269
DM, Hypertension	0.92(0.42 – 1.98)	0.822
Hypertension	6.9(2.13 – 22.3)	0.001**
Pathology		
IDC	25.69(0.71 – 934.81)	0.077
ILC	1(reference)	
PR		
Negative	1.22(0.48 – 3.1)	0.671
Positive	1 (reference)	
HER2		
HER2-1	0.84(0.44 – 1.6)	0.6
HER2-2	1(reference)	
Ki67		
Low	1(reference)	0.107
High	1.54(0.91 – 2.59)	
Tumor size		
TI	1(reference)	0.28
T2	0.98(0.35 – 2.75)	0.968
T3	5.13(0.54 – 48.8)	0.155
Lymph node staging		
N0	1(reference)	**0.001****
NI	0.34(0.15 – 0.81)	0.014*
N2	0.25(0.13 – 0.51)	**<0.001****
N3	0.42(0.2 – 0.9)	0.026*
Stage		
I	1(reference)	0.726
II	29357.4(0 -)	0.882
III	23671.05(0 -)	0.885
Surgery		
MRM	1 (reference)	
BCS	1.83(0.85 – 3.93)	0.122
Chemotherapy		
AC &Taxol	1.67(0.71 – 3.96)	0.239
AC	1.73(0.95 – 3.16)	0.075
TC (4 Cycles)	1 (reference)	0.175
PCR		
No	27.87(3.8 – 204.36)	<0.001**
Yes	1 (reference)	
Overall Survival		
Variables	CHR (95% CI)	**p-value**
Residence		
Rural	1 (reference)	0.106
Urban	1.44(0.93 – 2.25)	
Menopausal		
Premenopausal	1 (reference)	0.291
Postmenopausal	1.27(0.81 – 1.99)	
Performance status		
0	1(reference)	0.061
I	1.8(1.11 – 2.92)	0.018*
II	1.29(0.46 – 3.63)	0.634

Disease Free survival		
Comorbidity		
No	1(reference)	0.054
Diabetes	2.26(1.05 – 4.84)	0.036*
DM, Hypertension	1.07(0.57 – 2.01)	0.844
Hypertension	2.22(1.04 – 4.73)	0.04*
Pathology		
IDC	23.04(0.49 – 1079.13)	0.11
ILC	1(reference)	
PR		
Negative	1.25(0.67 – 2.31)	0.485
Positive	1 (reference)	
HER2		
HER2-1	1.27(0.72 – 2.24)	0.402
HER2-2	1(reference)	
Ki67		
Low	1(reference)	0.012*
High	1.78(1.14 – 2.77)	
Tumor size		
I	1(reference)	0.255
2	2.82(1.02 – 7.79)	0.045*
3	0(0 -)	0.967
4	2.45(0.73 – 8.2)	0.145
Lymph node staging		
0	1(reference)	**0.025***
I	0.74(0.37 – 1.47)	0.388
2	0.47(0.27 – 0.8)	**0.005***
3	1.02(0.52 – 2)	0.967
Stage		
I	1 (reference)	0.927
II	0.99(0.57 – 1.71)	0.971
III	0.91(0.54 – 1.53)	0.709
Surgery		
MRM	1 (reference)	
BCS	1.03(0.49 – 2.14)	0.944
Chemotherapy		
AC &Taxol	0.71(0.22 – 2.31)	0.569
AC	0.56(0.16 – 1.89)	0.347
TC (4 Cycles)	1.46(0.38 – 1.89)	0.583
AC & DD Taxol	1 (reference)	0.175
PCR		
No	1 (reference)	<0.001**
Yes	41.31(4.87 – 350.2)	

IDC=invasive ductal carcinoma, ILC=invasive lobular carcinoma, ER=estrogen receptor, PR=progesterone receptor, HER2=human epidermal receptor, IHC=immunohistochemestry, MRM =modified radical mastectomy, BCS =breast conservative surgery, AC =adriamycime cyclophosphamide protocol, TC=taxotere cyclophosphamide protocol, DD=dose dense * Statistically significant ** Statistically highly significant CHR crude hazard ratio CI Confidence interval

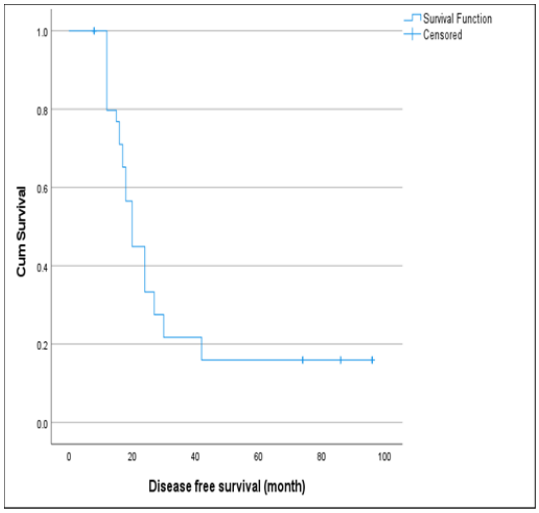
Table (5) Multivariate COX regression analysis for the predictor factors affecting the overall survival and disease-free survival among studied group:

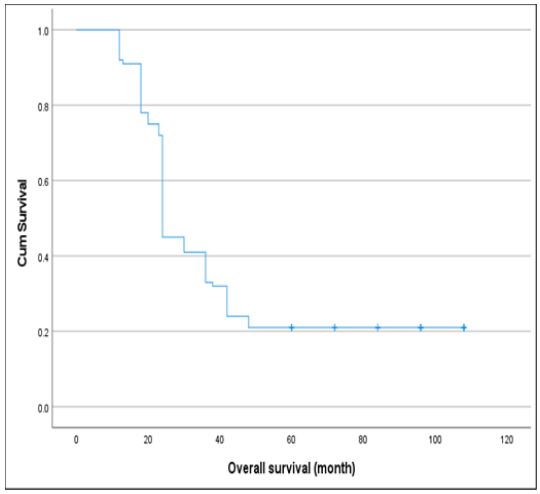
Variables	Overall survival	
	Hazard ratio (95% CI)	**p-value**
PS		
0	1 (reference)	0.001**
1	0.84(0.44 – 1.6)	0.594
2	0.03(0.01 – 0.2)	<0.001**
Ki 67		
Low	1(reference)	0.011*
High	2.3(1.22 – 4.3)	
Lymph node staging		
N0	1(Reference)	0.92
N1	0.89(0.37 – 2.16)	0.793
N2	0.82 (0.82 – 1.6)	0.553
N3	0.77(0.32 – 1.87)	0.565
Comorbidities		
Absent	1(Reference)	<0.001**
DM	2.1(0.71 – 6.19)	0.181
DM& HTN	0.41 (0.15 – 1.12)	0.083
HTN	11.99 (2 – 72)	0.007*
pCR (No)	1098996.65 (0 -)	0.931
Variables	**Progression free survival**	
	Hazard ratio (95% CI)	**p-value**
PS		
0	1 (reference)	0.001**
1	3.69(1.76 – 7.77)	
Lymph node staging		
N0	1(Reference)	0.008*
N1	0.5(0.18 – 1.21)	0.119
N2	0.4 (0.16 – 0.99)	0.046*
N3	0.17(0.06 – 0.46)	<0.001**
Comorbidities		
Absent	1(Reference)	<0.001**
DM	1.21(0.39 – 3.21)	0.831
DM& HTN	0.71 (0.28 – 1.81)	0.471
HTN	42.84 (8.63 – 212.67)	<0.001**
pCR (no)	31.51(3.95 – 251.67)	0.001**

pCR(pathological complete response)
* Statistically significant. ** Statistically highly significant AHR adjusted hazard ratio CI Confidence interval

Table (6) Disease free survival and overall survival among the studied patients:

Survival	Mean ± SD Median (IQR)
DFS (Months)	30.0±25.52 20 (8-96)
5-year DFS	59 (79.7%)
Survival	**Mean ± SD Median (IQR)**
OS (Months)	38.82±27.54 24 (12-108)
5-year OS	79 (79.0%)





(A) (B)

Figure 1: Kaplan-Meier curves for (A): disease free survival rate among the studied group, (B): overall survival rate among the studied group

DISCUSSION

The hormone receptor as well as the human epidermal growth factor receptor 2 statuses of tumors are crucial characteristics that guide therapy methods for breast cancer, which is a diverse illness with varied biology and therapeutic results. Low levels of human epidermal growth factor receptor 2 (HER2) protein expression are found in around 50% of breast tumors that do not have HER2 amplification. Uncertainty surrounds the therapeutic effects of HER2-low and NAC [12].

There are multiple studies with different conclusions regarding the effect of different subtypes of HER2 expression on NAC response [12; 13; 14]. A pooled analysis by the German research group showed that the pCR rate in HER2-low patients was lower than that in HER2-negative patients (29.2% vs 39.0%), and this difference was only present in the hormone receptor (HR)positive subgroup (17.5% vs 23.6%). However, this difference disappeared in the multivariate analysis [15]. Some studies have proposed opposite results, with a Brazilian study suggesting that HER2-low patients have a higher pCR rate in the HR-positive group (13% vs 9.5%), while there was no significant difference in the HR-negative group (51% vs

47%) [10]. Tarantino et al. considered that HER2-low had a lower pCR rate (17% vs 27%) but was not related to HR status [16]. The inconsistency of reported results may be caused by factors such as differences in population selection, race, therapeutic regimens, etc. [17]. Currently, it is important to determine if tumors with HER2-low-positive status exhibit distinct biological behavior and should be classified as a distinct genetic subtype, given the influence of HER2 status on NAC response and patient survival remains debatable.

This study revealed that the median age of the studied group was 49, but Alves et al. [12] showed that the median age at diagnosis of HER2 low BC women was 53 years. Also, Li et al. [17] showed that there was no association between age and HER2-low status, response, or survival

About half of them were postmenopausal and all of them were married (100.0%), In agreement with the current study Alves et al. [12] revealed that 56% of women with low HER2 BC were postmenopausal, Furthermore, de Moura Leite et al. [10] revealed that there was no association between menopausal status and HER2-low status.

Regarding the clinical data, the mean BMI of the patients was (34.3±4.9) ranging from 28.5 to 46.0. Also, we revealed that approximately all patients with BC were either overweight or obese, this agreed with the results demonstrated by Dehesh et al. [19] who found a significant association between obesity and the incidence of BC in a systematic review and meta-analysis.

In this study, most patients had PS 0, this agreed with Alves et al. [12] who revealed that the majority of their patients were PS 0 (93%), moreover, the study showed that there was no association between PS status and HER2-low status.

According to family history, 5% of the studied cases had a positive family history of BC, also Won et al. [20] in a nationwide study from Korea showed that there were 7% of women with BC have a positive family history.

In this study 28% of patients had comorbidities, however, Ewertz et al. [21] revealed that 16% of BC patients had comorbidities and the study showed that Overall, the risk of death was substantially raised for all comorbidities; however, the risk of death from BC was notably elevated only for peripheral vascular disease, chronic pulmonary disease, dementia, liver, and renal disorders.

IDC was the commonest pathological type (96.0%) followed by ILC (4.0%). This agreed with Alves et al. [12] who revealed that the majority of the studied cases (75.6%) had IDC followed by ILC (14.6%) in low HER2 BC. Our study also found a significant association between pathological type and HER2-low status.

Grade II is the commonest (73.0) followed by Grade III (27.0). This agreed with Alves et al. [12] who revealed that the majority of their patients were Grade II (50%) followed by Grade III (36%). Also, de Moura Leite et al [10] showed that most patients had Grade II(57.2 %) followed by Grade III (28.4%) disease

In this study, all patients (100.0%) were ER-positive, (85.0%) were PR-positive, and (56.0%) were low Ki67< 20%. In agreement with the current study, Mutai et al. [22] showed the majority of patients (70%) have a low proliferation index (Ki67% < 20%). However, Alves et al. [12] showed that 20% of patients with early BC had low Ki67. Moreover, both studies found no association between KI67 and HER2 low-status

Tumor size T2 was the commonest (78.0%) followed by tumor size T1 (10.0%). Alves et al. [12] showed that most of the cases (44.4%) were T2 followed by T3 (37.5%).

In this study, N2 was the commonest (39.0%) followed by N0 (33.0%) then N1 (16.0%), and lastly N3 (12.0%). However, Alves et al. [12] showed that most of the cases (40%) were N0 followed by N1 (36%).

Tumor stage II was the commonest (48.0%)

followed by stage III (46.0%) and lastly stage I (6.0%). In agreement with the current study, Collins et al. [18] showed that Tumor stage II was the most commonest (63.6%) followed by stage III (19.1%).

However, Alves et al. [12] showed that 55% of cases were stage III and 45% were stage II. [12]

Regarding treatment, the majority of the studied group (89.0%) had MRM and (11.0%) did BCS. In agreement with the current study, Alves et al. [12] showed that MRM was the commonest performed procedure in (40%) of cases followed by lumpectomy + SLNB (26%) and Mastectomy + SLNB (18%).

AC and weekly paclitaxel was the commonest chemotherapy regimen (62.0%) followed by AC (27.0%) then TC (8.0%) and lastly AC and DD paclitaxel (3.0%). Alves et al. [12] showed that the most common NAC regimen was AC followed by paclitaxel; 73.2% of patients were HER2-low; nevertheless, with no statistically significant difference between the two groups.

According to pathological response, our study showed that patients who achieved pCR were 16% only and 84% were not in pCR, in agreement with Alves et al. [12],14.6 % of the studied group achieved pCR and 85.4 % were not in pCR. Also, de Moura Leite et al. [10] showed that only 13% achieved pCR.

Concerning survival rate and time, the 5-year DFS rate among the studied group was (59.0%) with average (of 30±25.52) months ranging from (8-69) months while de Moura Leite et al. [10] showed 5 years 72% DFS in patients with HER2 low BC, Nonneville et al. [13] showed that the 3-year DFS was 81% after NAC in patients with HER2-low and Domergue et al. [10] showed 5-year DFS 63.99%.

The 5-year OS rate was (79.0%) among the studied group with an average (of 38.82±27.54) months ranging from (12 to 108) months, however, de Moura Leite et al. [10] revealed 89.4% 5 years OS, and Domergue et al. [10] showed 5-year OS 70% (95%Cl67.22;76.23).

The difference in outcome between studies may be due to the difference in patients' clinical/pathological features and treatment modality.

Univariate analysis of the parameters that predict pathological response revealed a statistically significant correlation between pathological response and pathological type. Low HER2 and other factors were related to the pathological response, although the relationship was not statistically significant.

Moreover, Alves et al. [12] revealed no patient demographic factors significantly predicted pCR to NAC and Baez-Navarro et al. [23] showed that age had a significant prediction of pCR.

In a univariate analysis of the predictor factors affecting the DFS among the studied group, it was revealed that there was a statistically significant impact on 5 years of DFS regarding menopausal status, PS, LN staging, and pathological response. Regarding other variables, there was no statistically significant association

Moreover, Collins et al. [18] showed that tumor staging was identified as a significant predictor for DFS in multivariable analysis, Burgos et al. [24] revealed that When compared to individuals with ILC, those with IDC had a longer DFS, suggesting that this diagnosis may be a positive prognostic factor for survival.

However, Li et al. [17] showed that the clinical stage, T stage, and N stage were independent predictors for DFS in multivariable analysis. However, they found no association between pathological type and DFS.

Also, Lee et al. [25] revealed that pathological type was not associated with the 2-year DFS, among young, aged BC, the contrast may be due to the difference in age group

The univariate analysis for the predictor factors affecting the 5-year OS among the studied group showed that there was a statistically significant impact on the OS regarding ki67status, tumor size, LN staging, and pathological response. While regarding

other variables, there was no statistically significant difference.

In agreement with the current study, Collins et al. [18] showed that tumor size was identified as a significant predictor for OS in multivariable analysis. While de Moura Leite et al. [10] revealed that pathological type was identified as a significant predictor of OS rate in multivariable analysis.

Moreover, Won et al. [20] showed that for HR-positive BC, advanced pathological stage, and histological grade III were associated with worse survival in multivariate analysis.

However, Elobaid et al. [26] showed that tumor grade and stage of cancer at presentation are jointly significantly associated with survival in the multiple Cox proportional hazard model. Also, Li et al. [17] showed that the clinical stage, T stage, and N stage were independent predictors for survival in multivariable analysis. However, they found no association between pathological type and survival.

The current study found no association between low HER2 and OS and DFS. Consistent with the present study findings, Alves et al. [12] demonstrated that HER2 status was not significantly associated with outcomes such as (DFS) ($p = 0.97$) or (OS) ($p = 0.35$).

The current study was limited by a small sample size, being a single-center study, and a relatively short follow-up period. Another drawback is that it is retrospective and does not include patients over a long enough time frame to account for the fact that different HER2 testing and interpreting protocols were in use at the time.

CONCLUSIONS

Our results did not show a significant impact of low HER2 on pCR, DFS, or OS, but showed low pCR achievement especially as most were HR-positive. Low HER2 may be a distinct biological entity that requires further research with a prospective nature and adequate population. With the new HER2 targeting ADCs which prove benefit in low HER-2 patient's preparatory activity data, patients with low HER2 may considered a special population subset for finding new treatment options to NAC to improve BC results.

Conflictsof Interest

The authors report no conflicts of interest.

Financial disclosure

None declared

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3):209-49.
2. Abdelaziz A. H, Shawki M. A, Shaaban A. M, Albarouki S. K, Rachid A. M, Alsalhani O. M, et al. Breast cancer awareness among Egyptian women and the impact of caring for patients with breast cancer on family caregivers' knowledge and behaviour. RESONCOL, 2021, 17(1), 1–8.
3. Dimitrakopoulos F. I. D, Kottorou A, Antonacopoulou A. G, Makatsoris T, Kalofonos H. P.. Early-stage breast cancer in the elderly: confronting an old clinical problem. Journal of breast cancer,2015, 18(3), 207-17.
4. Hu Z, Fan C, Oh DS, Marron JS, He X, Qaqish BF,et al. The molecular portraits of breast tumors are conserved across microarray platforms. BMC Genomics. 2006;7:96.
5. Vici P, Pizzuti L, Natoli C, Gamucci T, Di Lauro L, Barba M, et al. Triple positive breast cancer: a distinct subtype?. Cancer Treat. Rev,2015, 41(2), 69-76.
6. Ahn S, Woo JW, Lee K, Park SY. HER2 status in breast cancer: changes in guidelines and complicating factors for interpretation. J Pathol Transl Med. 2020;54(1):34-44.
7. Tarantino P, Hamilton E, Tolaney SM, Cortes J, Morganti S, Ferraro E, et al. HER2-Low Breast Cancer: Pathological and Clinical Landscape. J Clin Oncol.

2020;38(17):1951-62.
8. Badowska-Kozakiewicz AM, Budzik MP. Immunohistochemical characteristics of basal-like breast cancer. Contemp Oncol (Pozn). 2016;20(6):436-43.
9. Amin M. B, Greene F. L, Edge S. B, Compton C. C, Gershenwald J. E, Brookland R. K, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population‐based to a more "personalized" approach to cancer staging. CA: CA Cancer J Clin 2017, 67 (2), 93-9.
10. De Moura Leite L, Cesca MG, Tavares MC, Santana DM, Saldanha EF, Guimarães PT, et al. HER2-low status and response to neoadjuvant chemotherapy in HER2 negative early breast cancer. Breast Cancer Res Treat. 2021;190(1):155-63.
11. Litière S, Collette S, de Vries EG, Seymour L, Bogaerts J. RECIST - learning from the past to build the future. Nat Rev Clin Oncol. 2017;14(3):187-92.
12. Alves FR, Gil L, Vasconcelos de Matos L, Baleiras A, Vasques C, Neves MT, et al. Impact of Human Epidermal Growth Factor Receptor 2 (HER2) Low Status in Response to Neoadjuvant Chemotherapy in Early Breast Cancer. Cureus. 2022;14(2):e22330.
13. De Nonneville A, Houvenaeghel G, Cohen M, Sabiani L, Bannier M, Viret F, et al. Pathological complete response rate and disease-free survival after neoadjuvant chemotherapy in patients with HER2-low and HER2-0 breast cancers. Eur J Cancer. 2022;176:181-8.
14. Domergue C, Martin E, Lemarié C, Jézéquel P, Frenel JS, Augereau P, et al. Impact of HER2 Status on Pathological Response after Neoadjuvant Chemotherapy in Early Triple-Negative Breast Cancer. Cancers (Basel). 2022;14 (10):2509.
15. Denkert C, Seither F, Schneeweiss A, Link T, Blohmer JU, Just M, Wimberger P, et al. Clinical and molecular characteristics of HER2-low-positive breast cancer: pooled analysis of individual patient data from four prospective, neoadjuvant clinical trials. Lancet Oncol. 2021;22(8):1151-61.
16. Tarantino P, Jin Q, Tayob N, Jeselsohn RM, Schnitt SJ, Vincuilla J,et al. Prognostic and Biologic Significance of ERBB2-Low Expression in Early-Stage Breast Cancer. JAMA Oncol. 2022;8 (8):1177-83.
17. Li Y, Maimaitiaili A, Qu F, Li G, Shi B, Wang Y, et al. Effect of HER2-low-positive status on neoadjuvant chemotherapy and survival outcome of breast cancer: a 10-year dual-center retrospective study. Am J Cancer Res. 2023;13(8):3571-581.
18. Collins PM, Brennan MJ, Elliott JA, Abd Elwahab S, Barry K, Sweeney K,et al. Neoadjuvant chemotherapy for luminal a breast cancer: Factors predictive of histopathologic response and oncologic outcome. *Am J Surg*. 2021;222(2):368-76.
19. Dehesh T, Fadaghi S, Seyedi M, Abolhadi E, Ilaghi M, Shams P, et al. The relation between obesity and breast cancer risk in women by considering menstruation status and geographical variations: a systematic review and meta-analysis. BMC Womens Health. 2023;23(1):392.
20. Won HS, Ahn J, Kim Y, Kim JS, Song JY, Kim HK,et al. Clinical significance of HER2-low expression in early breast cancer: a nationwide study from the Korean Breast Cancer Society. Breast Cancer Res. 2022;24(1):22.
21. Ewertz M, Land LH, Dalton SO, Cronin-Fenton D, Jensen MB. Influence of specific comorbidities on survival after early-stage breast cancer. Acta Oncol. 2018;57(1):129-34.
22. Mutai R, Barkan T, Moore A, Sarfaty M, Shochat T, Yerushalmi R, et al. Prognostic impact of HER2-low expression in hormone receptor positive early breast cancer. Breast. 2021;60:62-9.
23. Baez-Navarro X, van Bockstal MR, Jager

A, van Deurzen CHM. HER2-low breast cancer and response to neoadjuvant chemotherapy: a population-based cohort study. Pathology. 2024;56(3):334-42.
24. Burgos C. H, Parra L. B, Ferrández M. S, Valiente L. Á, Chapinal B. G, Vozmediano M. A., et al. Comparative survival analysis of infiltrating ductal carcinoma versus infiltrating lobular carcinoma of the breast. EJS,2024, 200
25. Lee J, Kim SH, Kim Y, Park J, Park GE, Kang BJ. Radiomics Nomogram: Prediction of 2-Year Disease-Free Survival in Young Age Breast Cancer. Cancers (Basel). 2022;14(18):4461.
26. Elobaid Y, Aamir M, Grivna M, Suliman A, Attoub S, Mousa H, et al. Breast cancer survival and its prognostic factors in the United Arab Emirates: A retrospective study. PLoS One. 2021; 16 (5): e0251118.

Citation:
Mohamed, A., Elfaragy, O., Abdelwahab, F., Abdelrahman, A. Impact of Low HER2 Expression on Neoadjuvant Treatment Response in Early Luminal Breast Cancer. *Zagazig University Medical Journal*, 2024; (4355-4370): -. doi: 10.21608/zumj.2024.313346.3524