RESEARCH ARTICLE

Prognostic value of basal markers (epidermal growth factor receptor "EGFR" and cytokeratin 5/6) expression in triple-negative invasive breast cancer

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Abstract

Objective: The To distinguish between basal and non-basal subtypes of triple-negative breast cancers based on epidermal growth factor receptor and cytokeratin 5/6, and to establish the association of the diagnosis with clinicopathological parameters and survival rates.

Methods: The retrospective study was conducted at the Clinical Oncology and Nuclear Medicine Department of Kafrelsheikh University Hospital and Tanta University Hospital, Egypt, and comprised medical records from January 2014 to December 2018 related to cases with histopathologically proven triple-negative breast cancer who had been treated and followed up for at least 5 years. The cases had been evaluated using immunohistochemistry for epidermal growth factor receptor and Cytokeratin 5/6 expression. Data related to prognostic factors, overall survival and disease-free survival was retrieved. Data was analysed using SPSS 21.

Results: There were 100 patients with median age 50 years (inter-quartile range: 35-55.25 years; range: 22-69 years). There were 58(58%) pre-menopausal subjects, 15(15%) had positive family history, and 68(68%) had tumour size T2. Basal markers were noted in 74(74%) patients. Basal subtype was significantly more common in patients aged <50 years at diagnosis, premenopausal women, patients with positive nodal status, those with grade III tumours, and patients with Ki67 proliferation marker >20% ($p<0.05$). Tumour size, histological subtypes and lympho-vascular invasion were not significantly different between the groups ($p>0.05$). The basal subtype had worse disease-free survival and overall survival rates ($p<0.05$).

Conclusion: Triple-negative breast cancer patients who expressed epidermal growth factor receptor and/or cytokeratin 5/6 were found to have poor findings, with worse disease-free survival and overall survival.

Keywords: Breast neoplasms, Ki67 antigen, EGFR Receptors, Oncology. **DOI: 10.47391/JPMA.EGY-S4-33**

Introduction

Breast cancer (BC) is the most prevalent cancer in women, and the fifth most common reason of cancer-related mortality globally. BC accounts for around 1 in 4 cancer diagnoses, and 1 in 6 cancer deaths among women.[1]

Triple-negative breast cancer (TNBC) is distinguished by the lack of three therapeutically significant BC biomarkers: progesterone receptor (PR), oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2). It accounts for 10-20% of all BCs.[2] Five-year survival rate for TNBC cases is much lower compared to those for non-TNBC cases regardless of the diagnostic stage.[3] This is due to the absence of targeted therapy options and the high tendency of TNBC to spread to organs like the lungs and the brain.[4] It is also more prevalent in premenopausal young women and those with the breast cancer gene 1 (BRCA1) gene mutation, has a higher grade and mitotic index, is diagnosed at a later stage, and has a poorer prognosis.[5]

In TNBC classification, Cytokeratin 5/6 (CK5/6) and/or epidermal growth factor receptor (EGFR)-positive BCs are categorised as basal-like BCs (BLBCs), whereas CK5/6 and EGFR-negative BCs are categorised as non-basal-like BCs (NBLBCs).[6] TNBC classification by gene expression subtype is critical in clinics. Immunohistochemistry (IHC) analysis for BLBC is the most extensively acknowledged method for identifying alternative biomarkers, such as EGFR and CK5/6. Therefore, screening for CK5/6 and EGFR is required for determining TNBC prognosis and treatment strategy.[7]

CK5/6 is a crucial molecular marker for the identification of TNBC of the basal subtype and may be an independent prognostic factor for TNBC.[8]

EGFR, a member of the erbB family of casein kinase receptor protein, plays a critical role in tumour cell proliferation process, involving cell movement, tissue invasion and angiogenesis. Also, usage of anti-HER-1 antibodies or blockers of HER-1 tyrosine kinase may also be beneficial.[6]

A study found a significantly lower response of BLBC to chemotherapy compared to NBLBC, as well as an increased

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recurrence and worse prognosis risk.[6]

The current study was planned to distinguish between basal and non-basal subtypes of TNBCs based on EGFR and CK5/6, and to establish the association of the diagnosis with clinicopathological parameters and survival rates.

Patients and Methods

The retrospective study was conducted at the Clinical Oncology and Nuclear Medicine Department of Kafrelsheikh University Hospital and Tanta University Hospital, Egypt, and comprised patient records from January 2014 to December 2018.

After approval from the ethics review committee of Kafrelsheikh University Hospital, Egypt, medical records were retrieved of histopathologically proven TNBC cases aged >18 years who had received neoadjuvant chemotherapy and adjuvant chemotherapy with residual invasive disease on pathological testing who had active status ≤2 as defined by the Eastern Cooperative Oncology Group (ECOG).[9] All the case had been followed up for at least 5 years.

Patients with tumour size 4 (T4) BC (the chest wall and/or the skin directly affected by the tumour having ulceration or macroscopic nodules), recurrent or metastatic disease, bilateral BC, pregnancy, altered mental status, secondary malignancy and uncontrolled medical disease were excluded.

An informed written consent had been obtained from each participant after which they had been subjected to detailed history as well as clinical examination and laboratory investigations. Radiological examination, such as mammography and ultrasonic examination of breast and axilla and/or magnetic resonance imaging (MRI) of the breast, plain X-ray chest (CXR) and or computed tomography (CT) was done as and when needed, Pelvi-abdominal ultrasound and/or CT scan, bone scan, if indicated, and echocardiography were also done selectively.

Before neo-adjuvant chemotherapy (NAC), histological specimens of BC were obtained by core biopsy and analysed with IHC staining for ER, PR, HER 2 and protein Ki67. The histological type and grade of the tumour were identified. A high proliferative rate Ki67 patient was defined as a positive staining rate of 20% or above. IHC was performed on formalin-fixed paraffin-embedded slices with an optimal thickness of 4mm glued to positively charged slides. Stained slides for EGFR and CK5/6 were prepared. After deparaffinisation and rehydration in graded alcohols to distilled water, tissue slices were incubated in 3% hydrogen peroxide for 10 minutes. Antigen retrieval was accomplished by soaking slides in acetic acid and microwaving them at 95°C for 30 minutes, after which they were allowed to cool at room temperature and subsequently washed with phosphate-buffered saline (PBS). Primary antibodies were used for overnight incubation of the slides at room temperature for EGFR (Diagnostic Bio Systems: Species rabbit, clone SP9, Isotype IgG1/kappa) and CK5/6 (Bio Genex: Species rabbit, clone EPR1600Y, Iso type IgG). Using the streptavidin-biotin complex detection technique, the staining was finished. After applying 3,3□-Diaminobenzidine (DAB) for 10-15 minutes, the reaction was stopped by applying distilled water. Negative control slides were produced by omitting the main antibody and substituting PBS that was included in each run. On 10 randomly selected areas of each slide, the proportion of immunopositivity for EGFR and CK5/6 was determined.

EGFR was evaluated as +ve if >1% of tumour cells displayed membrane reactivity, whereas CK5/6 was counted as +ve if any cytoplasmic and/or membranous staining was seen.[10]

Histopathology was performed after NAC to identify tumour size, lymph node (LN) status, type of histological histopathology and grade, presence of lympho-vascular invasion (LVI), and IHC for ER, PR, HER 2 and Ki67.

All cases had received breast conserving surgery (BCS) or modified radical mastectomy (MRM) with axillary dissection.

For NAC, doxorubicin was provided at a dosage of 60mg/m^2, cyclophosphamide 600mg/m^2 every 21 days for four cycles, and taxanes for additional four cycles as weekly paclitaxel 80mg/m^2 or three weekly doses of docetaxel 100mg/m^2.

Chemotherapy response was determined by clinical examination and breast ultrasonography, which were done 3 times: before NAC, after adriamycin/cyclophosphamide (AC)), and after paclitaxel. Based on Response Evaluation Criteria in Solid Tumours (RECIST), patients were divided into two categories: those who had a complete response or partial response, and those who did not respond (NR) or progressed (PD). Tumour length by tumour breadth was used to calculate size (cm^2).[11]

The pathological response was categorised as either complete response (pCR) or disease persistence. The pCR was defined as the absence of invasive breast and axillary LN tumours.

Adjuvant chemotherapy was given to cases with residual disease in the breast or LNs after NAC in the shape of oral capecitabine 1250mg/m^2 of body-surface area, twice per day, on days 1 to 14 every 3 weeks for 6 cycles.

Regarding radiotherapy, 6 Mev Linear Accelerator was used

for all cases. The breast, chest wall and nodal fields received a dose of 45-50Gy in 1.8-2.0Gy per fraction five times a week over a 5-6 weeks in conventional fractionation. Hypo-fractionated schedules involved 40-42.5Gy/2.66Gy/fx daily, and for BCS cases, a boost to the tumour bed was suggested.

Disease-free survival (DFS) was expressed from the time of therapy until the time of disease recurrence, distant metastasis, or death if no recurrence or metastasis occurred. Overall survival (OS) was calculated from the diagnosis date to the death date or last follow-up.

All cases had been followed up for 5 years; every 3 months in the first two years, and every 6 months for another three years. Follow-up check-ups included clinical examination, laboratory investigations using cancer antigen 15-3 (CA15-3) and radiological investigation.

Primary outcome was the prevalence of basal markers EGFR and CK5/6 by IHC expression in TNBC and its correlation with different prognostic factors. Secondary outcomes were DFS and OS of all patients with TNBC and its correlation with the two basal markers.

The sample size was calculated using G*Power 3.1.9.2.[12] Assuming the recurrence of the tumour as 55.7%-88%, according to a study[13], the calculations were done with 0.05 alpha (α) error and 95% power. A few cases were added to cover up for possible dropouts.

Data was analysed using SPSS 21. Qualitative data was presented as frequencies and percentages. Chi- square test was used for analysis as appropriate. Kaplan-Meier and multivariate analysis were done. Two-tailed $p<0.05$ was considered statistically significant.

Results

There were 100 patients with median age 50 years (inter-quartile range [IQR]: 35-55.25 years; range: 22-69 years). There were 58(58%) pre-menopausal subjects, 15(15%) had positive family history, and 68(68%) had tumour size T2. Basal markers were noted in 74(74%) patients (Table 1).

EGFR and/or CK5/6) were mostly of the basal subtype (Figures 1-2), while 26(26%) cases did not test +ve for either marker (Table 2).

Basal subtype was significantly more common in patients aged <50 years at diagnosis, premenopausal women, patients with positive nodal status, those with grade III tumours, and patients with Ki67 proliferation marker>20% ($p<0.05$). Tumour size, histological subtypes and LVI were not significantly different between the groups ($p>0.05$) (Table 3).

The 2-year OS was 49(66.2%) and 26(100 %) for basal and non-basal TNBCs, respectively. The 5-year OS was 45(60.8%) and 22(84.6%) for the two groups, respectively ($p=0.019$). The 2-year DFS was 48(64.8%) and 24(92.3%) for basal and non-basal TNBCs, respectively. The 5-year DFS was 48(64.8%) and 22(84.6%) for two types, respectively ($p=0.043$) (Figure 3).

For all patients, the 2-year OS was 75(75%) and the 5-year OS was 67(67%). The overall 2-year DFS was 72(72%)

Table-1: Patient characteristics.

Characteristics		n (%)
Basal or non basal type	Basal	74 (74.00)
Androgen state	Non basal	26 (26.00)
Age group	<50 Years	52 (52.00)
Age group	>50 Years	48 (48.00)
PS	ECOG <2	78 (78.00)
PS	ECOG 2	22 (22.00)
Family History	Positive	15 (15.00)
Family History	Negative	85 (85.00)
Menopausal State	Pre-Menopausal	58 (58.00)
Menopausal State	Post-Menopausal	42 (42.00)
Pathology	IDC	88 (88.00)
Pathology	ILC	12 (12.00)
Tumour Size	T1	8 (8.00)
Tumor Size	T2	68 (68.00)
Tumor Size	T3	22 (22.00)
Lymph Node State	N+ve	87 (87.00)
Lymph Node State	N-ve	13 (13.00)
Grade	Grade I	1 (1.00)
	Grade II	42 (42.00)
Grade	Grade III	57 (57.00)
Ki 67	<20 %	21 (21.00)
Ki 67	>20%	79 (79.00)
Lymph Vascular Invasion	Positive	35 (35.00)
Lymph Vascular Invasion	Negative	65 (65.00)
Surgery	MRM	56 (56.00)
Surgery	BCS	44 (44.00)
Chemo Therapy	Done	100 (100.00)
Chemo Therapy	Not Done	0 (0.00)
Radio Therapy	Done	99 (99.00)
Radio Therapy	Not Done	1 (1.00)
Pathological response	PCR	23 (23.00)
Chemo Therapy	Non PCR	77 (77.00)

PS: Performance status, ECOG: Electrocorticography, IDC: Infiltrating ductal carcinoma, **ILC:** Invasive lobular carcinoma, **BCS:** Breast conserving surgery, MRM: Modified radical mastectomy, pCR: Pathological complete response.

Table-2: Immunohistochemical (IHC) expression of basal markers in triple-negative breast cancer (TNBC) cases.

Immunohistochemical basal marker	n (%)
EGFR+ and/or CK 5/6 +	74%
- EGFR + CK 5/6 +	37 (37%)
- EGFR + CK 5/6 –	13 (13%)
- EGFR - CK 5/6 +	24 (24%)
EGFR - CK 5/6 -	26 (26%)

EGFR: Epidermal growth factor receptor, CK 5/6: Cytokeratin 5/6.

Table-3: Immunohistochemical (IHC) expression of basal markers in triple-negative breast cancer (TNBC) cases.

	Total (n = 100) n (%)	Non basal (n = 26) n (%)	Basal (n = 74) n (%)	Test of sig.	*p-value*
Age (years)					
≤50	52 (52.0)0	6 (23.1)	46 (62.2)	X2=11.776	0.001*
>50	48 (48.0)	20 (76.9)	28 (37.8)		
Min. – Max.	22.0 - 69.0	30.0 - 69.0	22.0 - 64.0	t= 2.857	0.005*
Mean ± SD.	48.95 ± 10.02	53.62 ± 8.65	47.31 ± 10.01		
Family history					
Negative	85 (85.0)	21 (80.8)	64 (86.5)	X2=0.493	0.528
Positive	15 (15.0)	5 (19.2)	10 (13.)5		
Menopausal state					
Pre	58 (58.0)	10 (38.5)	48 (64.9)	X2=5.506	0.019*
Post	42 (42.0)	16 (61.5)	26 (35.1)		
Pathology					
IDC	88 (88.0)	22 (84.6)	66 89.2	0.381	0.504
ILC	12 (12.0)	4 (15.4)	8 (10.8)		
Tumour Size					
T1	8 (8.0)	3 (11.5)	5 (6.8)	1.770b	0.421
T2	68 (68.0)	15 (57.7)	53 (71.6)		
T3	24 (24.0)	8 (30.8)	16 (21.6)		
Lymph Node State					
N0	13 (13.0)	8 (30.8)	5 (6.8)	10.305	0.013*
N1	36 (36.0)	10 (38.5)	26 (35.1)		
N2	35 (35.0)	5 (19.2)	30 (40.5)		
N3	16 (16.0)	3 (11.5)	13 (17.6)		
Grade					
G1	1 (1.0)	1 (3.8)	0 (0.0)	14.285	<0.001*
G2	42 (42.0)	18 (69.2)	24 (32.4)		
G3	57 (57.0)	7 (26.9)	50 (67.6)		
Ki 67					
law	21 (21.0)	10 (38.5)	11 (14.9)	χ2=6.457	0.012*
high	79 (79.0)	16 (61.5)	63 (85.1)		
Lymph Vascular Invasion					
Negative	65 (65.0)	17 (65.4)	48 (64.9)	0.002	0.962
Positive	35 (35.0)	9 (34.6)	26 (35.1)		

X2: Chi-square Test, b: Monte-Carlo test, t: Independent t-test,
SD: Standard deviation, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma.
*Statistically Significant

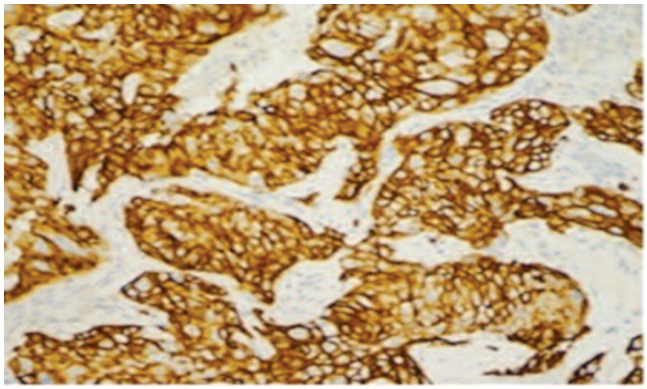

Figure 1: A case of basal-like breast cancer (BLBC) showing strong membranous epidermal growth factor receptor (EGFR) expression (Immunoperoxidase X 200).

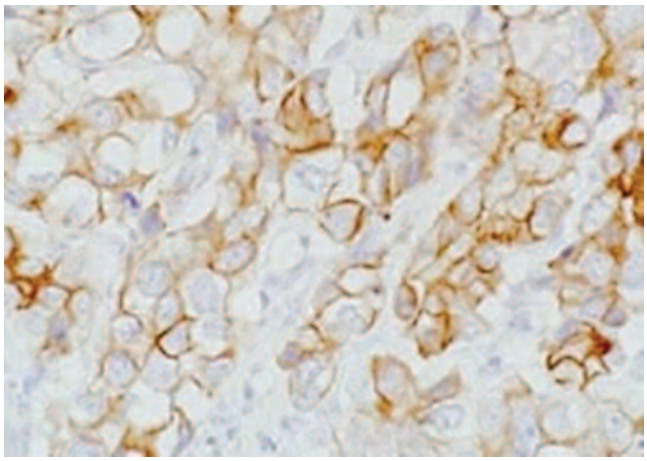

Figure 2: A case of basal-like breast cancer (BLBC) showing moderate cytoplasmic and membranous Cytokeratin 5/6 (CK 5/6) expression (Immunoperoxidase X 400).

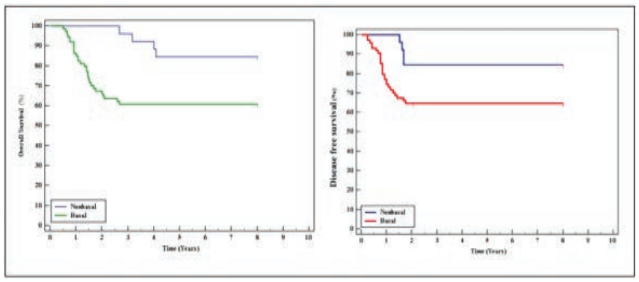

Figure 3: Correlation between overall survival (OS) and disease-free survival (DFS) across triple-negative breast cancer (TNBC) basal or non-basal subtypes.

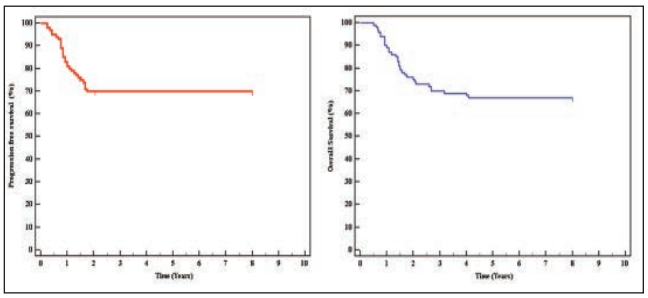

Figure 4: Kaplan-Meier survival curve for overall survival (OS) and disease-free Survival (DFS).

and the 5-year DFS was 70(70%) (Figure 4).

Discussion

TNBCs have been reported to have a much poorer prognosis than other BC types kinds of BC.(14) TNBCs have a faster proliferation rate that metastasises rapidly to the brain, liver, and lungs, and afflict younger individuals more frequently than do the other BC subtypes.(15) EGFR and CK5/6 are globally recognised biomarkers for the detection of BLBC.[16]

In the current study, BLBC before NAC accounted for 74% cases, of which CK5/6 and/or EGFR +ve expressions

accounted for 61% and 50%, respectively, while double expression was observed in 37% patients with CK5/6 prevalence. An earlier study found that the most TNBC cases had basal subtype tumours with prominent EGFR expression.[10]

The genetically-defined BLBC is the most prevalent subtype of TNBC, accounting for 70-80% cases, and it has been suggested that instead of the gene chip, IHC detection should be performed to identify genetically-determined BLBC.[17]

In the current study, the most prevalent age group was <50 years (52%), followed by >50 years (48%), and the overall mean age was 48.9 years. The age of TNBC observed by Tan et al.[18] was >40 years and the mean age determined by Rao C et al., was 46.8 years.[10,18] Also, Pistelli et al. discussed that at diagnosis 42% cases were aged <50 years.[19]

Regarding the current findings, EGFR and CK5/6 were significantly correlated with age. This was in contrast with Rao C et al. who found an nonsignificant correlation between the two.[10]

Patients with +ve family history accounted for about 15% in the current study, while Tariq et al. found that cases with +ve family history constituted about 30.77% cases.[20]

Most of the patients in the current study (88%) were diagnosed with invasive ductal carcinoma (IDC), whereas the remaining patients (12%) had invasive lobular carcinoma (ILC). These findings are comparable to those of Mc Ghan et al., who reported IDC in 86% cases.[21]

In contrast to the current findings, studies reported that any histological subtype of BC can be TNBC, with potential effects on their pathogeneses, progressions and prognosis.[22, 23]

In the current study, patients with tumour size at presentation >2cm (T2) constituted 68% of the cases, which similar to earlier findings.[24] Moreover, the current study revealed a nonsignificant correlation between the tumour size and the expression of basal markers. The matter has also been reported upon earlier.[10, 18]

Most of the TNBC patients in the current study were grade 3 (57%) and significantly correlated with basal subtype. This is in line with literature.[10]

Also, in agreement with the findings, studies reported that poorly differentiated tumours constituted about 47%, which may be due to higher grades and invasive pattern.[10, 25]

In the current study, patients with +ve LVI were 35% compared to 41% reported earlier. This may be due to the small sample size of the size compared to that of the earlier study which had 344 patients.[26]

The current study assessed high expression of Ki67 in 79% cases, which is similar to the reported data.[27]

Also, in the current study, 63% patient having high Ki67 levels were of the basal subtype, with a significant correlation with the basal markers, which is similar to findings reported in literature.[12, 27]

OS and DFS were significantly worse in basal subtype than the non-basal subtype in the current study, which is consistent with earlier reports, which may be due to the bad prognosis instead of destructive chemotherapy.[16]

Foulkes et al. also noticed that TNBC cases with EGFR, CK5/6, or both, showed a bad prognosis compared to TNBCs that lacked expression of both the markers.[4]

Also, Conforti R et al. observed that the basal group had low chemotherapy benefits than the negative group for basal markers.[4, 24]

Conclusion

TNBC patients who expressed EGFR, CK5/6 or both had poor findings with worse OS and DFS. The basal markers should be recognised in clinical practice.

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