Original Article

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Pathology Section

EGFR Expression and its Association with Molecular Subtypes of Breast Carcinoma: A Cross-sectional Study

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ABSTRACT

Introduction: The incidence of breast carcinoma is rising worldwide. The Epidermal Growth Factor Receptor (EGFR) is a tyrosine kinase receptor that serves as an independent prognostic marker of poor clinical outcomes and aggressiveness in breast carcinoma. EGFR overexpression is specific to Triple-Negative Breast Cancer (TNBC). Therefore, the suppression of EGFR could potentially enhance the efficacy of TNBC treatment.

Aim: To estimate the expression of EGFR in breast carcinoma and determine whether it is associated with aggressiveness (especially its correlation with tumour grade and proliferation index) and molecular subtyping based on Immunohistochemistry (IHC).

Materials and Methods: This was a cross-sectional observational study conducted at Murshidabad Medical College and Hospital, Berhampore, West Bengal, India, from December 2022 to May 2024. A total of 31 confirmed breast carcinoma cases were studied. An IHC analysis was performed using biomarkers for Oestrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal growth factor Receptor 2 (HER2/neu), and Ki67 for molecular subtyping, along with EGFR to establish associations with subtypes. Results were analysed using the Chi-square test with Statistical Package for the Social Sciences (SPSS) version 20.0.

Results: During the study period, 31 cases were examined, with a mean age of 54.91 years. Eleven cases (35.48%) showed EGFR overexpression. EGFR was significantly associated with grade 3 tumours (p-value=0.01) and a high Ki67 index (p-value=0.04).

Conclusion: This study indicated that EGFR expression is an independent indicator of tumour aggressiveness. Its association with TNBC suggests that EGFR suppression therapy may be a preferred treatment option for TNBC.

Keywords: Breast cancer treatment, Epidermal growth factor receptor, Molecular subtypes

INTRODUCTION

The breasts are highly modified apocrine sweat glands composed of skin and subcutaneous fibrofatty tissue and rest on the pectoralis major muscles, separated by a fascial layer [1]. According to Globocan data from 2020, breast carcinoma accounts for 13.5% of all cancer cases in India and 10.6% of all cancer-related deaths, with a cumulative risk of 2.8 [2]. Breast cancer is rarely found in women under the age of 25 years, as its incidence rapidly increases after the age of 30 years. Apart from being predominantly a female concern (approximately 99% of patients are female), other major risk factors include hereditary factors such as oestrogen exposure, while environmental and lifestyle factors are less significant. Breast carcinoma is a heterogeneous disease with distinct molecular subtypes that exhibit different biological behaviours [3]. Previously, ER, PR and human EGFR 2 (HER2) were predictive markers of systemic therapy responses and are now recognised as the primary determinants of breast cancer biology, helping to refine molecular and prognostic subtyping.

Currently, both conventional and novel molecular techniques are routinely used in practice to help diagnose morphologically challenging entities [4]. Microarray profiling of invasive breast carcinoma has identified subtypes of morphologically similar breast carcinomas (Luminal A, Luminal B, HER2 positive and Triple Negative) [5]. EGFR is part of a large cell surface receptor family, known as the ErbB family, which includes four subtypes: EGFR (ErbB1/Her1), ErbB2 (Her2), ErbB3 (Her3), and ErbB4 (Her4) [6]. EGFR, also known as c-erbB-1 or Her1 in humans, is located on the short arm of chromosome 7 (7p12). Its downstream signaling pathways, including PI3K, Ras-Raf-MAPK, and JNK, are activated to promote cell proliferation, invasion and angiogenesis while protecting cells against apoptosis [7]. EGFR overexpression is observed in 15-45% of breast cancer cases [8]. This overexpression is associated with larger tumour sizes, poor differentiation and poor clinical outcomes.

While EGFR expression is not correlated with lymph node involvement in breast carcinoma, it is observed in all breast cancer subtypes, particularly in TNBC and Inflammatory Breast Cancer (IBC), which are aggressive. The overexpression of EGFR is inversely correlated with hormone receptor status. Treatment of TNBC subtypes has been challenging due to a lack of established clinically relevant treatment targets. Despite findings suggesting that EGFR overexpression indicates poor prognosis, previous studies focused on targeting EGFR in breast cancer have yielded disappointing results [9], highlighting the need for further research on expression levels.

The overexpression of EGFR protein specific to TNBC often increases the resistance of these cancer cells to conventional hormone therapies. Therefore, suppression of EGFR has the potential to enhance the efficacy of TNBC treatment [10]. This study was designed to identify the association between EGFR expression and tumour grading and proliferation index [11], as well as its relationship with molecular subtypes to assess prognosis and treatment efficacy.

MATERIALS AND METHODS

An institutional-based cross-sectional observational study was conducted in the Department of Pathology, in collaboration with the Department of General Surgery at Murshidabad Medical College and Hospital, Berhampore, West Bengal, India. The study spanned one and a half years, from December 2022 to May 2024. Ethical clearance was obtained from the Institutional Ethical Committee (ECR/1620/Inst/WB/2021), and informed consent was acquired from the study population.

Inclusion criteria: Clinically and histopathologically confirmed breast carcinoma cases admitted to Murshidabad Medical College and Hospital during the study period were included in the study.

Exclusion criteria: Breast carcinoma cases that did not consent to participate, whose surgical specimen receptor status was unavailable or remained equivocal and all stromal tumours of the breast were excluded from the study.

Study Procedure

Tissue samples from all cases that fulfilled the inclusion and exclusion criteria were sent to the Pathology Department for routine histopathological examination and, subsequently, immunohistochemical examination. All tissue samples were collected in 10% buffered formalin and processed for routine histopathological examination. Grossing and reporting suggestive of breast carcinoma were conducted according to the College of American Pathologists (CAP) protocol [12]. Histopathological diagnosis was made by cutting 5 µm thick sections from formalin-fixed paraffin-embedded blocks and staining them with Haematoxylin and Eosin (H&E). The study evaluated epidemiological parameters, histopathological findings, histopathological grade of carcinoma, aggressiveness by proliferation index and IHC findings. The classification of the histopathological grade was based on Modified Bloom-Richardson grading [13].

Immunohistochemistry: Histopathologically confirmed breast carcinoma tissues underwent further analysis using IHC biomarkers. The positivity of IHC expression was reported using a standard scoring pattern. The clone for ER rabbit monoclonal antibody was EP1, for PR it was EP2 rabbit monoclonal antibody, for HER2Neu it was EP3 rabbit monoclonal antibody, for Ki67 it was MIB1 mouse monoclonal antibody, and for EGFR it was 31G7 mouse monoclonal antibody.

The study examined the association of EGFR expression with histopathological grade, proliferation index and molecular subtypes of breast carcinoma. For IHC staining, 3 µm thick sections from formalin-fixed paraffin-embedded tissues were placed on poly-L-lysine coated slides. IHC staining was performed manually, following the steps outlined in the supplied kit.

ER/PR interpretation was considered positive with at least 1% positive cells and quantification was performed using the Allred scoring system [14]. HER2Neu immunostaining was conducted according to ASCO/CAP guidelines. For HER2Neu interpretation, scores of 2+ (complete, intense, circumferential membrane staining in ≤10% of invasive tumour cells) and 3+ (complete, intense, circumferential membrane staining in >10% of invasive tumour cells) were classified as positive [15]. A case of gastric adenocarcinoma known to be HER2 positive served as the positive control, while negative control was achieved by omitting the primary antibody.

For present study, any degree of brown nuclear stain was considered a positive cell for Ki67 index interpretation. Cytoplasmic brown staining was not counted as a positive tumour cell. The Ki67 index was calculated as the number of positive tumour cells divided by the total number of tumour cells, multiplied by 100 [16]. EGFR-positive staining appeared as a linear to finely granular pattern in the cell membrane and adjacent cytoplasm, or as coarsely granular cytoplasmic staining. An adenocarcinoma lung specimen known to be EGFR positive was used as a positive control. EGFR interpretation was considered positive with at least 1% positive cells with weak intensity [17].

STATISTICAL ANALYSIS

For statistical analysis data were entered into MS Excel. For descriptive purposes, the mean, range and percentage were used. The Chi-square test was used to determine the significance of the study using SPSS version 20.0. The significance level was set at a p-value <0.05.

RESULTS

The majority of the 29 cases (93.55%) were Invasive Breast Carcinoma of No Special Type (IBC-NST), while mucinous and metaplastic carcinoma each accounted for one case (3.22%). All cases involved female patients. The most commonly affected age group was 41-60 years, comprising 23 cases (74.2%), followed by the 61-80 years age group with seven cases (22.6%), one case (3.2%) was of 21-40 years age group. The mean age at presentation was 54.91 years.

In this study, 11 cases (35.50%) showed EGFR overexpression. Among the 31 cases, 21 were Grade 2 tumours (67.70%), and 10 were Grade 3 tumours (32.30%) [Table/Fig-1]. According to TNM staging, the majority of tumour masses (19 cases, 61.29%) were in the T2 stage, followed by T3 (10 cases, 32.26%), and T4 (2 cases, 6.45%). Among the 31 cases, 26 (83.80%) exhibited lymphovascular invasion (LVSI), and 16 (51.60%) cases had lymph nodal involvement.

Parameters	EGFR positive	EGFR negative	p-value
Grade 2 tumour	4 (12.90%)	17 (54.84%)	0.013
Grade 3 tumour	7 (22.58%)	3 (9.68%)	

[Table/Fig-1]: Association of EGFR with MBR grading of tumour, Ki67 index, molecular subtypes.

Immunohistochemical findings: In this study, it was observed that the majority (13 cases, 41.90%) were Triple-Negative Breast Cancer (TNBC), followed by 7 cases (22.60%) of Luminal B, six cases (19.40%) of HER2-enriched, and 5 cases (16.10%) of Luminal A subtype [Table/Fig-2]. A total of 15 cases (48%) had a high Ki67 index [Table/Fig-3].

Parameters	EGFR positive	EGFR negative	p-value
TNBC positive	8 (25.81%)	5 (16.13%)	0.021
TNBC negative	3 (9.68%)	15 (48.39%)	
Luminal A positive	1 (3.23%)	4 (12.90%)	0.631
Luminal A negative	10 (32.23%)	16 (51.61%)	
Luminal B positive	1 (3.23%)	6 (19.35%)	0.372
Luminal B negative	10 (32.23%)	14 (45.16%)	
HER2 enriched positive	1 (3.23%)	5 (16.13%)	0.383
HER2 enriched negative	10 (32.23%)	15 (48.39%)	

[Table/Fig-2]: Association of EGFR with molecular subtypes.

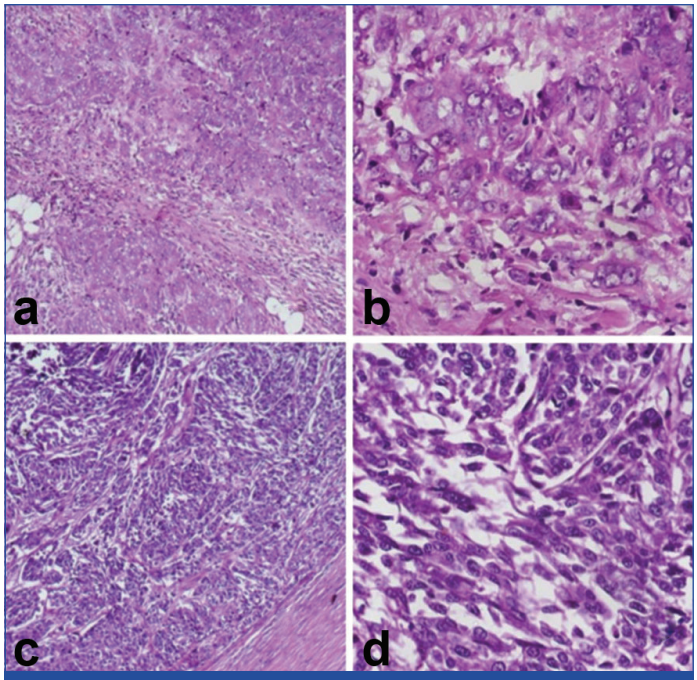
Parameters	EGFR positive	EGFR negative	p-value
<30%Ki67 index	3 (9.68%)	13 (41.94%)	0.044
>=30%Ki67 index	8 (25.81%)	7 (22.58%)	

[Table/Fig-3]: Association of EGFR with Ki67 index.

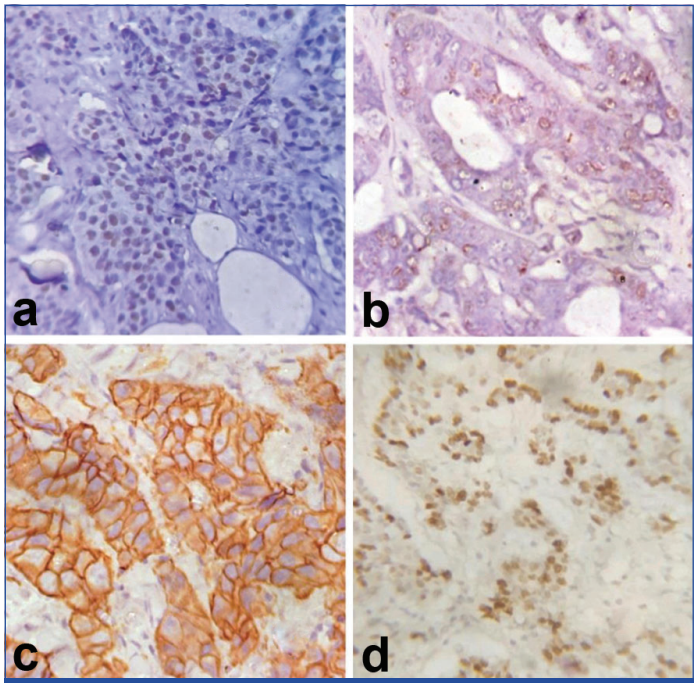
EGFR findings: Out of the 11 EGFR-positive cases, four were Grade 2 and seven were Grade 3 tumours. Conversely, of the 20 EGFR-negative cases, 17 were Grade 2 and three were Grade 3 [Table/Fig-1]. There was a significant association between EGFR expression and high-grade tumours (p-value=0.01) [Table/Fig-1]. Among the 11 cases, three had a Ki67 index of less than 30%, while eight had a Ki67 index of 30% or greater. There was a significant association between EGFR expression and a high proliferation index, indicating more aggressive tumours (p-value=0.04) [Table/Fig-3]. Out of the 11 EGFR-positive cases, eight were TNBC, while each of the Luminal B, Luminal A, and HER2-enriched cases represented one case. There was a significant association between EGFR expression and TNBC, an aggressive type of breast carcinoma (p-value=0.02) [Table/Fig-2]. Microphotograph of IBC-NST, ER, PR, HER2, Ki67 is shown in [Table/Fig-4-6].

DISCUSSION

Breast cancers can present in various clinical forms, such as hard, irregular breast lumps, skin changes and nipple changes [18].



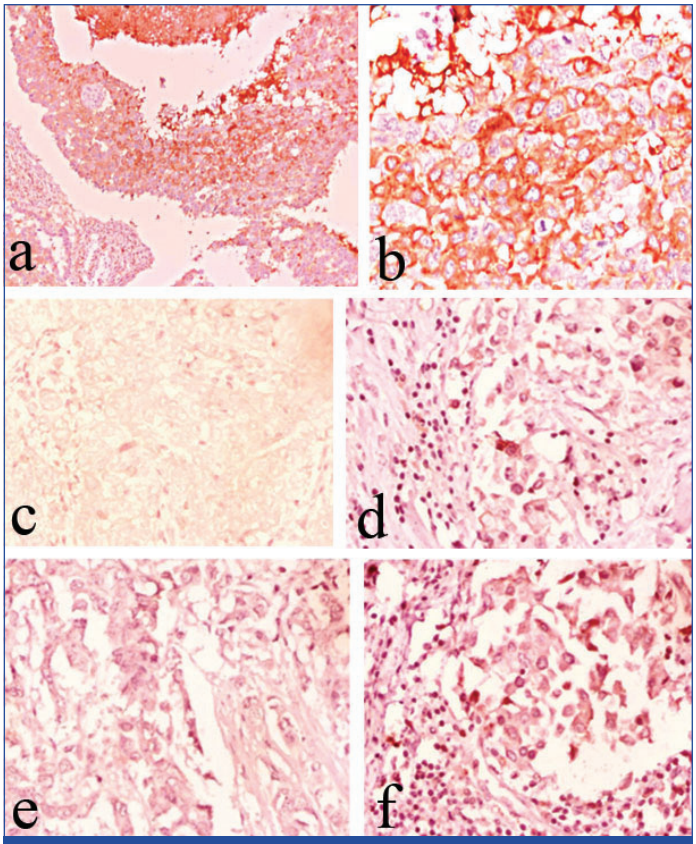
[Table/Fig-4]: Microphotograph of (a) IBC-NST, (NHS Grade2); H&E (100x) (b) IBC-NST, (NHS Grade2), H&E (400x); (c) IBC-NST (NHS Grade 3, (H/E stain 100x); and (d) IBC-NST (NHSGrade3), Haematoxylin and Eosin (H/E) stain (400x).



[Table/Fig-5]: HP microphotographs of: a) ER positivity, 400x; b) PR positivity 400x; c) HER 2 Neu Positivity, 3+(400x); d) Ki67 immunostain 10% in IBC-NST (400x).

Traditional prognostic factors for breast carcinoma include histologic grade, TNM stage and the Nottingham Prognostic Index. However, IHC-based molecular classification of breast carcinoma also serves as both prognostic and predictive markers [19]. A discussion of breast cancer subtypes would be incomplete without considering the influence of gene expression signatures as subtype classifiers [20].

Targeting ER is the first line of treatment for hormone-positive breast cancer cases, while HER2-targeted therapy is used for HER2-positive types. Unfortunately, there is currently no targeted therapy available for TNBC [21]. EGFR overexpression often increases the resistance of TNBC cancer cells to conventional hormone therapies. Thus, EGFR suppression has the potential to enhance treatment efficacy for this subtype [10]. It has been reported that EGFR overexpression is an indicator of poor prognosis [11]. Therefore, this study aimed to identify the association of EGFR expression with the grading and proliferation index of breast carcinoma for prognostic purposes, as well as its relation to molecular subtypes for treatment efficacy.



[Table/Fig-6]: a) Microphotograph of IBC-NST (NHS Grade 3) EGFR immunostain strong positive in IBC-NST (100x); b) Microphotograph of IBC-NST (NHS Grade 3) EGFR immunostain strong positive in IBC-NST, (400x); c) Microphotograph of EGFR immunostain moderate positive in IBC-NST, (100x), IBC-NST, (NHS Grade 2); d) Microphotograph of EGFR immunostain moderate positive in IBC-NST, (400x), IBC-NST, (NHS Grade 2); e) Microphotograph of EGFR immunostain weak positive in IBC-NST,(100x), IBC-NST, (NHS Grade2); f) Microphotograph of EGFR immunostain weak positive in IBC-NST, (400x), IBC-NST, (NHS Grade 2).

In the present study, a total of 31 patients were included, all of whom were females. The age range was from 21 to 80 years, with the most common age group affected being 41-60 years (74%) and a mean age of 54.91 years. Malvia S et al., observed that trends for 5-year age distribution among different registries showed a peak relative proportion of breast carcinoma between 45 and 49 years in all registries in India [22]. This study supports that observation. According to data from Breast Cancer India (BCI), the average age for developing BC has experienced a significant left shift in recent decades, with a drastic increase in incidence among individuals aged 25 to 40 years [23].

From this study, we found that 29 cases (94%) were IBC-NST, along with one case of mucinous carcinoma and one case of metaplastic carcinoma. Makki J, stated that invasive ductal carcinoma is the most common form (55%) of invasive breast cancer [24]. A study by Anderson WF et al., also showed that 68.5% of total cases were IBC-NST [25].

In this study, 68% of tumours (21 cases) were classified as Grade 2 (Modified Bloom-Richardson grading). A recent study by Ravikumar G and Ananthamurthy A, found that 67.5% of cases were classified as MBR Grade 2, which supports present study findings [26]. Ahmed Z et al., reported that 75.83% of cases were Grade 2, and 20% were Grade 3 in their study [27]. In the present study, tumour sizes ranged from 20 mm to 125 mm. Most patients had tumours in the T2 stage (19 patients, 61%), followed by T3 (32%), and then T4 (7%). Ahmed Z et al., found that 44.16% of cases were T2, 41.66% were T3, and 6.66% were T4 [27]. Kashyap D et al., observed a mean size of breast carcinoma at 3.5 cm, with 65.1% of tumours measuring between 2-5 cm [28]. In the present study, 61% of tumours fell within the 2-5 cm range.

In an immunohistochemistry marker study, it was observed that 13 patients (42%) had TNBC, followed by the Luminal B subtype (23%),

HER2-enriched subtype (19.4%), and Luminal A subtype (16.1%). Li J et al., found 35.6% Luminal A, 35.6% Luminal B, 13.7% TNBC, and 15.2% HER2-enriched types in their study. In the present study, the percentage of TNBC tumours was higher [29]. Lu B et al., stated that approximately 15% to 20% of all breast cancers are TNBCs [30]. Kim MJ et al., in their study of 776 consecutive cases of breast carcinoma, found that the incidence of the triple-negative subtype was 30% [31].

In the present study, EGFR was expressed in 11 cases (35.48%) among the 31 cases examined. Changavi AA et al., stated that EGFR is expressed in 15-45% of breast cancers, which supports our findings [8]. Rimawi MF et al., found that 18% of cases expressed EGFR [9]. This study showed a positive association (p-value=0.01) between high-grade breast carcinoma and EGFR expression, which aligns with the findings of Changavi AA et al., that also showed a positive correlation (p-value=0.03491) between these factors [8].

The present study did not show any association between EGFR expression and Lymphovascular Space Invasion (LVSI) features, nor axillary lymph nodal involvement, similar to other studies. Changavi AA et al., found that EGFR was predominantly expressed in TNBC (89.47%) in their study, reporting a positive correlation (p-value=0.000583) with TNBC types [8]. In present study, eight out of 13 TNBC cases (61.53%) were EGFR positive, and a positive association (p-value=0.02) was noted. Gumuskaya B et al., also suggested that EGFR is mostly expressed in TNBC (61.40%) [32], which was consistent with the present study. However, Ali Naeem H et al., showed that 80% of non TNBC types had EGFR expression in their study, which is not supported by our findings [33].

Shawarby MA et al., showed that EGFR is expressed in breast carcinomas with a high proliferation index (Ki67) [34]. Present study also found a positive association (p-value=0.04) between EGFR expression and a high Ki67 index.

Limitation(s)

The sample size was small, comprising only 31 cases; therefore, larger population-based studies are needed. In this study, molecular classification of breast carcinoma and EGFR expression were assessed based on IHC, not by microarray analysis or EGFR gene amplification, which are considered standard methods.

CONCLUSION(S)

The most common carcinoma type is invasive breast carcinoma of no special type. It can be suggested that EGFR is an independent prognostic marker of poor clinical outcome and aggressiveness in breast carcinoma. The TNBC subtype is considered to be more aggressive than other subtypes. Thus, this study suggests that EGFR suppression therapy may be a treatment of choice for the TNBC subtype.

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