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Pathology Section

Clinicopathological Spectrum and Expression of Basal Markers CK5/6 and EGFR in Triple-Negative Breast Cancer: A Cross-sectional Study

DIVYA RADHAKRISHNAN[1], SANGEETHA K NAYANAR[2], ASWATHI KRISHNAN[3], RATHEESAN KUMBAKARA[4]

ABSTRACT

Introduction: Triple-Negative Breast Cancer (TNBC) is a biologically diverse disease identified through Immunohistochemistry (IHC) and defined as the absence of Oestrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2) expression. This subtype is very aggressive and associated with poor clinical outcomes, underscoring the importance of precise and timely diagnosis to guide effective treatment. Morphological and molecular profiling can help classify TNBC into various subtypes, each with distinct prognostic implications and potential therapeutic responses. Among these subtypes, breast carcinoma expressing basal phenotype is one of the most studied groups, due to their poor prognosis.

Aim: To evaluate the proportion of basal like phenotype in TNBC based on surrogate immunopanel Cytokeratin 5/6 (CK5/6) and/or Epidermal Growth Factor Receptor (EGFR).

Materials and Methods: The cross-sectional study was conducted at Clinical Laboratory Services and Translational Research Oncopathology Division, Malabar Cancer Centre Postgraduate Institute of Oncology Sciences and Research, Thalassery, Kerala, India, from April 2021 to July 2021. The data were collected retrospectively from January 2017 to December 2020. A total of 83 female patients with triplenegative primary Invasive Breast Carcinoma (IBC) were selected, based on the ER, PR and the HER-2 immunophenotype. Histopathological data such as tumour subtype, tumour size, tumour grade, Ductal Carcinoma In-situ (DCIS), necrosis, Tumour Infiltrating Lymphocyte (TIL) and Immunohistochemical (IHC) data including ER, PR, HER2/neu, Ki-67 of patients were retrieved from the documented Pathology reports. IHC (EGFR, CK5/6) was done for those cases. Clinical data was obtained from medical records. A statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 20.0. The Chi-square test was applied to assess the relationship between the IHC markers and variables such as tumour subtype, tumour grade, DCIS, necrosis, TIL.

Results: Out of the 83 TNBCs, 61 cases (73.5%) were positive for CK5/6 and 53 cases (63.9%) were positive for EGFR. The mean age of the patients was 55 years with standard deviation 12.3. The predominant histological type was Invasive Breast Carcinoma No Special Type (IBC NST). A statistically significant association between EGFR expression and tumour grade was observed with a p-value of 0.04. Among them, 32 cases (38.6%) had Ki-67 proliferation index more than 50%.

Conclusion: The present study reaffirms the high prevalence of basal-like markers in TNBC and suggests their expression is largely independent of tumour size, grade necrosis, DCIS, and TILs. Statistically significant association was found with increasing tumour grade (p=0.04). Routine IHC evaluation of EGFR and CK5/6 may aid in subtyping TNBC and can be helpful in developing targeted therapies, especially as clinical trials of anti-EGFR agents advance. The consistent presence of TILs in all cases reinforces their relevance in TNBC immunobiology, potentially helping therapeutic decisions involving immune checkpoint inhibitors.

Keywords: Cytokeratin 5/6, Epidermal growth factor receptor, Immunohistochemistry, Ki-67, Tumour grade, Tumour infiltrating lymphocyte

INTRODUCTION

Breast cancer has emerged as the most frequently diagnosed cancer among women globally, recently surpassing lung cancer, with approximately 2.3 million new cases reported annually. This increasing burden necessitates a comprehensive understanding of the disease and the development of effective therapeutic strategies. Breast cancer is a complex, heterogeneous disease influenced by environmental exposures, hormonal factors, genetic mutations, lifestyle, and nutritional habits. Consequently, patients present with diverse clinical, pathological, and molecular profiles [1].

At the 13th St. Gallen International Breast Cancer Conference (2013), breast cancer was categorised into luminal A, luminal B (HER2-negative/positive), HER2-enriched, and triple-negative subtypes [2]. TNBC is a biologically aggressive subtype lacking expression of ER, PR, and HER2 by IHC, limiting therapeutic options. TNBC is frequently observed in younger women and is commonly associated with BRCA1 (Breast Cancer gene 1) mutations [3]. TNBC comprises approximately 10-15% of all breast cancer cases [4,5].

Although TNBC is identified through IHC, molecular profiling has uncovered considerable heterogeneity within this group [6]. Based on gene expression patterns, TNBC can be further subdivided into several molecular subtypes: Basal-Like 1 (BL1), BL2, Immunomodulatory (IM), Mesenchymal (M), Mesenchymal Stem-Like (MSL), and normal-like [7]. A majority of TNBC cases fall within the basal-like category and although frequently overlapping with triple negativity, represents a distinct molecular entity [8,9].

Basal-Like Breast Cancers (BLBCs) exhibit high histological grade, elevated mitotic rate, and a distinct morphological pattern, including squamous metaplasia, necrosis, and dense lymphocytic infiltration [10,11]. Histological variants include medullary, atypical medullary,

myoepithelial, and metaplastic carcinomas [11,12]. These tumours commonly express basal cytokeratins (CK5/6, CK14, and CK17), EGFR, vimentin and have variable expression of smooth muscle actin, p63, CD117, CD10 and P-cadherin [11,13].

Gene expression profiling remains the gold standard for BLBC diagnosis, but due to practical limitations, IHC markers serve as surrogates. A four-marker panel (ER, HER2, EGFR, and CK5/6) offers 55-76% sensitivity and 100% specificity in identifying BLBCs [13]. Carey LA et al., refined this to define BLBC as ER-/PR-/HER2-, and CK5/6 and/or EGFR-positive [9]. BLBCs often harbour BRCA1 and TP53 mutations [14,15].

The present study with EGFR and CK5/6 as surrogate IHC markers was undertaken in study centre because the classification helps to identify tumours more accurately and potentially guide targeted therapy especially in resource limited setting where molecular profiling is not feasible and economical to all patients. The primary objective of the study was to evaluate proportion of TNBCs with basal phenotype based on surrogate immunopanel (CK5/6, EGFR); and the secondary objective were to analyse histomorphological spectrum and Ki-67 proliferation index of TNBCs.

MATERIALS AND METHODS

The cross-sectional study was conducted at Clinical Laboratory Services and Translational Research- Oncopathology Division, Malabar Cancer Centre Postgraduate Institute of Oncology Sciences and Research, Thalassery, Kerala, India, during the period from April 2021 to July 2021. A total of 83 female patients with triple-negative primary IBC were selected, based on the ER, PR and the HER-2 immunophenotype. The study was approved by the Institutional Ethics Committee (No.1617/IEC-ERC/13/MCC).

Inclusion and Exclusion criteria: Patients with biopsy and IHC proven Triple negative IBC were included in the study. Patients whose archived paraffin blocks were inadequate for performing IHC were excluded.

Study Procedure

Histopathological and IHC data of patients was retrieved from the archived Pathology reports. Clinical data was obtained from medical records. IHC for EGFR and CK5/6 were done on the archived paraffin blocks by manual method. The antibody clones which were used were: EGFR (EP22, PathnSitu) and CK5/6 (EP24/EP6, PathnSitu). This study assessed CK5/6 and EGFR expression in TNBCs using IHC and correlated these with clinicopathological features including age, tumour size, histologic grade, DCIS, necrosis, Tumour-Infiltrating Lymphocytes (TILs), and Ki-67 proliferation index. Cytokeratin 5/6 was scored as positive if any cytoplasmic and / or membranous staining was observed in the invasive component. EGFR was scored as positive if more than 1% of the tumour cells showed membrane staining [16].

STATISTICAL ANALYSIS

The data were entered and analysed by using SPSS version 22.0. The frequencies and the percentages of all the variables were computed. The Chi-square test was used to compare the association between the expressions of EGFR and CK5/6 and the macroscopic features such as tumour size and microscopic characteristics such as tumour grade, necrosis, TILs, DCIS of the tumours. The results were considered statistically significant if the p-value was <0.05.

RESULTS

A total of 83 cases of TNBCs were included in the study. As explained in [Table/Fig-1], majority of patients were aged above 50 years 53 (63.9%) cases, followed by those in the 40-50 years age group 17 (20.5%) cases, while 13 patients (15.7%) were younger than 40 years. Histopathologically, IBC-NST constituted the predominant subtype, accounting for 77 cases (92.8%). Special variants were uncommon, with metaplastic carcinoma observed in five cases (6%) and IBC-NST with medullary-like features in one case (1.2%). With respect to tumour size, most cases were categorised as T2 (2.1-5 cm), comprising 52 cases (62.7%). T1 tumours (0-2 cm) were identified in 15 cases (18.1%), while 16 cases (19.3%) presented as T3 tumours (>5 cm), indicating that a substantial proportion of patients presented with relatively larger tumour sizes. On histological grading, a predominance of high-grade tumours was noted. Grade III tumours constituted 49 cases (59.0%), whereas 34 cases (41.0%) were Grade II, reflecting the aggressive morphological profile typically associated with TNBCs. Assessment of TILs revealed that the majority of tumours demonstrated mild lymphocytic infiltration (56 cases, 67.5%), followed by moderate infiltration in 23 cases (27.7%), with only a small proportion showing higher degrees of lymphocytic response. Overall, the study predominantly comprised older patients with high-grade, intermediate-sized invasive carcinomas of no special type, with most tumours exhibiting mild TIL expression.

Parameters	n (%)
Age groups (in years)	
<40	13 (15.7%)
40-50	17 (20.5%)
>50	53 (63.9%)
Tumour subtype	
IBC-NST	77 (92.8%)
IBC-NST Medullary-like	1 (1.2%)
Metaplastic carcinoma	5 (6%)
Tumour size	
T1 (0-2 cm)	15 (18.1%)
T2 (2.1-5 cm)	52 (62.7%)
T3 (>5 cm)	16 (19.3%)
Tumour grade	
II	34 (41.0%)
III	49 (59.0%)
TIL	
Mild	56 (67.5%)
Moderate	23 (27.7%)
Dense	4 (4.8%)
Ki-67	
<50%)	51 (61.4%)
>50%)	32 (38.6%)
Necrosis	
Absent	60 (72.3%)
Present	23 (27.7%)
DCIS	
Absent	64 (77.1%)
Present	19 (22.9%)

[Table/Fig-1]: Distribution of demographic and pathologic variables in Triple Negative Breast Cancer (TNBC).

In the present study, EGFR expression was observed in 53 (63.9%) cases and CK5/6 expression in 61 (73.5%) cases of TNBC, indicating a high prevalence of basal marker positivity in the study as shown in [Table/Fig-2]. On evaluating the association between basal marker expression and age groups (<40 years, 40-50 years, and >50 years), a higher number of positive cases were noted in patients older than 50 years. However, statistical analysis using the Chi-square test demonstrated no significant association between age and EGFR expression (p=0.324), CK5/6 expression (p=0.230), or basal phenotype (p=0.440) as detailed in [Table/Fig-3]. Thus, although basal marker positivity was more frequently observed in the older age group, though it was not statistically significant suggesting

that basal phenotype expression in TNBC is independent of patient age in this study population.

The association of EGFR, CK5/6 expression, and basal phenotype with different tumour subtypes (IBC-NST, IBC-NST medullary-like and metaplastic carcinoma) is demonstrated in [Table/Fig-4]. The majority of cases belonged to IBC-NST and showed higher positivity for EGFR (49 cases), CK5/6 (58 cases), and basal phenotype (62 cases). However, when analysed using the Chi-square test, no statistically significant association was observed between tumour subtype and EGFR expression (p=0.741), CK5/6 expression (p= 0.185), or basal phenotype (p=0.478), as all p-values were greater than 0.05. This indicates that the expression of basal markers does not significantly differ across tumour subtypes in this study population. Similarly, [Table/Fig-5] evaluates the association between these markers and tumour size (T1, T2, and T3). Although higher marker positivity was observed in T2 tumours compared to T1 and T3, statistical analysis revealed no significant association between tumour size and EGFR expression (p=0.875), CK5/6 expression (p=0.201), or basal phenotype (p=0.646).

IHC	EGFR	CK5/6
Negative	30 (36.1%)	22 (26.5%)
Positive	53 (63.9%)	61 (73.5%)

[Table/Fig-2]: Frequency of EGFR and CK5/6 Expression in Triple Negative Breast Cancer (TNBC).

A statistically significant association was observed between EGFR expression and tumour grade (p=0.046), indicating that EGFR positivity was more frequently observed in Grade II tumours (26/34) compared to Grade III tumours (27/49), and this difference was statistically significant (p=0.046) [Table/Fig-6]. In contrast, CK5/6 expression (p=0.409) and basal phenotype (p=0.277) did not show a statistically significant association with tumour grade, although a higher number of Grade III tumours demonstrated positivity for these markers. No statistically significant association was found between EGFR expression (p=0.503), CK5/6 expression (p=0.542), or basal phenotype (p=0.298) and the presence or absence of necrosis shown in [Table/Fig-7]. Although marker positivity was numerically higher in tumours with necrosis, the differences were not statistically significant.

The association of EGFR and CK5/6 expression and basal phenotype with the presence of DCIS demonstrated in [Table/Fig-8]. No statistically significant association was observed between DCIS and EGFR expression (p=0.538), CK5/6 expression (p=0.540), or basal phenotype (p=0.944) on Chi-square analysis. Although marker positivity was numerically more frequent in cases without DCIS compared to those with DCIS, the differences were not statistically significant, indicating that the presence of an in situ component did not correlate with basal marker expression in this study. The association of EGFR and CK5/6 expression and basal phenotype with TILs categorised as mild, moderate, and dense is shown in [Table/Fig-9]. There was no statistically significant

Age group (years)	EGFR		p-value	CK5/6		p-value	Basal phenotype		p-value
	Positive	Negative		Positive	Negative		Positive	Negative	
<40	7	6	0.324	8	6	0.230	9	4	0.440
40-50	9	8		15	8		15	2	
>50	37	16		38	16		42	11	

[Table/Fig-3]: Association of EGFR and CK5/6 expression and basal phenotype with age group.
#Chi-square test applied

Tumour subtype	EGFR		p-value	CK5/6		p-value	Basal phenotype		p-value
	Positive	Negative		Positive	Negative		Positive	Negative	
IBC-NST	49	28	0.741	58	19	0.185	62	15	0.478
IBC-NST-Medullary like	1	0		1	0		1	0	
Metaplastic carcinoma	3	2		2	3		3	2	

[Table/Fig-4]: Association of EGFR and CK5/6 expression and basal phenotype with tumour subtype.
#Chi-square test applied

Tumour size	EGFR		p-value	CK5/6		p-value	Basal phenotype		p-value
	Positive	Negative		Positive	Negative		Positive	Negative	
T1	9	6	0.875	11	4	0.201	11	4	0.646
T2	33	19		41	11		43	9	
T3	11	5		9	7		12	4	

[Table/Fig-5]: Association of EGFR and CK5/6 expression and basal phenotype with tumour size.
#Chi-square test applied

Tumour grade	EGFR		p-value	CK5/6		p-value	Basal phenotype		p-value
	Positive	Negative		Positive	Negative		Positive	Negative	
Grade II	26	8	0.046	26	8	0.409	29	5	0.277
Grade III	27	22		35	14		37	12	

[Table/Fig-6]: Association of EGFR and CK5/6 expression and basal phenotype with tumour grade.
#Chi-square test applied

Necrosis	EGFR		p-value-	CK5/6		p-value	Basal phenotype		p-value
	Positive	Negative		Positive	Negative		Positive	Negative	
Present	16	7	0.503	18	5	0.542	20	3	0.298
Absent	37	23		43	17		46	14	

[Table/Fig-7]: Association of EGFR and CK5/6 expression and basal phenotype with necrosis.
#Chi-square test applied

DCIS	EGFR		p-value	CK5/6		p-value	Basal phenotype		p-value
	Positive	Negative		Positive	Negative		Positive	Negative	
Present	11	8	0.538	15	4	0.540	15	4	0.944
Absent	42	22		46	18		51	13	

[Table/Fig-8]: Association of EGFR and CK5/6 expression and basal phenotype with DCIS.
#Chi-square test applied

TIL	EGFR		p-value	CK5/6		p-value	Basal phenotype		p-value
	Positive	Negative		Positive	Negative		Positive	Negative	
Mild	34	22	0.454	39	17	0.494	42	14	0.257
Moderate	17	6		19	4		21	2	
Dense	2	2		3	1		3	1	

[Table/Fig-9]: Association of EGFR and CK5/6 expression and basal phenotype with Tumour Infiltrating Lymphocytes (TIL).
#Chi-square test applied

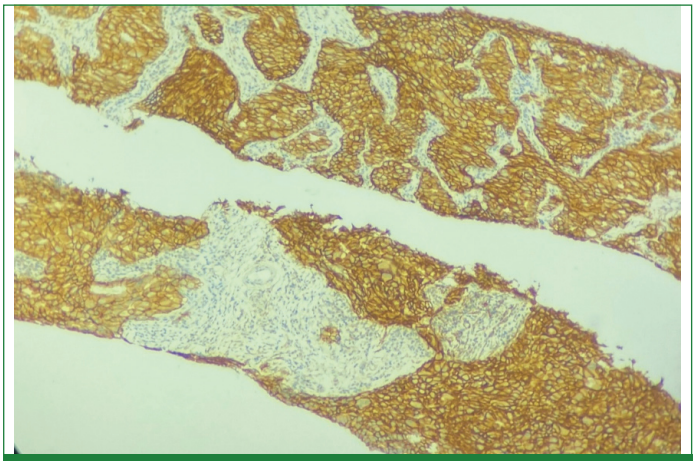
association between TIL density and EGFR expression (p=0.454), CK5/6 expression (p=0.494), or basal phenotype (p=0.257).

The association between Ki-67 proliferation index and basal phenotype is shown in [Table/Fig-10]. Statistical analysis using the Chi-square test demonstrated no significant association between Ki-67 expression and basal phenotype (p=0.803).

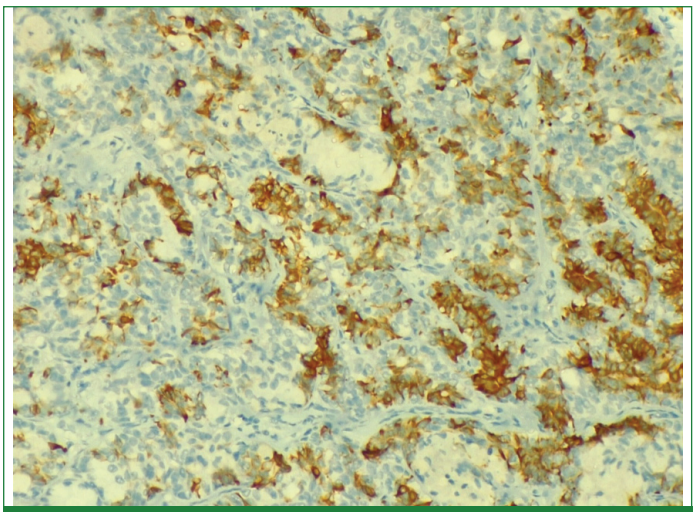
Ki-67	Basal phenotype		p-value
	Positive	Negative	
<50%	41	10	0.803
>50%	25	7	

[Table/Fig-10]: Association of Ki-67 with basal phenotype.

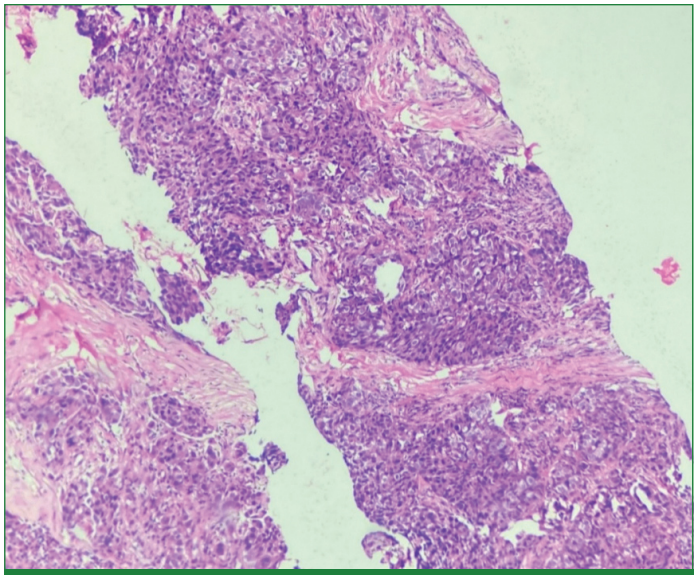
Representative IHC images demonstrating EGFR and CK5/6 staining are presented in [Table/Fig-11,12], respectively. Representative histological image of IBC-NST is given in [Table/Fig-13].



[Table/Fig-11]: IHC expression of EGFR with circumferential complete membrane staining, (400x).



[Table/Fig-12]: IHC expression of CK5/6, (400x).



[Table/Fig-13]: Histological Image showing Invasive Breast Carcinoma, No Special Type (H&E, 400x).

DISCUSSION

The TNBC represents a biologically aggressive form of breast carcinoma, defined by the lack of expression of ER, PR, and HER2. A considerable proportion of TNBC cases exhibit a basal-like immunophenotype, characterised by positive IHC staining for EGFR and/or cytokeratin 5/6 (CK5/6) [16]. The current study findings indicate a substantial overlap between triple-negative status and basal-like features; however, basal marker expression alone cannot reliably serve as a surrogate for triple negativity. This observation is consistent with the conclusions of Rakha EA et al., and Choccalingam C et al., [8,17].

Evaluation of EGFR and CK5/6 expression by IHC in a retrospective analysis of 83 TNBC cases diagnosed between January 2017 and December 2020 was done. Of these, 79.5% (66/83) demonstrated positivity for at least one basal marker- either EGFR or CK5/6. CK5/6 was expressed in 73.5% (61/83), while EGFR was positive in 63.9% (53/83) of cases. These findings are consistent with previous studies reporting frequent EGFR expression in TNBC [18].

The association between basal marker expression and various tumour characteristics, including size, grade, necrosis, DCIS, and TILs were further evaluated. While no significant correlations were found between the basal phenotype and most morphological or prognostic features, a statistically significant association was observed between EGFR expression and tumour grade.

Patients over the age of 50 accounted for 63.9% of the study population. Although basal marker expression was numerically higher in patients aged >50 years, no statistically significant association with age was observed. This trend aligns with previous studies suggesting that basal-like TNBC is more prevalent among younger women and may constitute a biologically distinct subgroup [9].

Most tumours in the cohort were of intermediate size (T2: 2.1-5 cm), accounting for 62.7% of cases, while smaller (T1: ≤2 cm) and larger tumours (T3: >5 cm) constituted 18.1% and 19.3%, respectively. Basal marker expression was noted across all tumour size categories. EGFR expression was most commonly observed in T2 tumours (33 out of 52), with CK5/6 and the combined basal phenotype also showing the highest frequency in this group. However, no statistically significant association was found between tumour size and basal marker expression (p >0.05), suggesting that basal marker expression likely emerges early in tumour development and is independent of tumour size [8].

Histologically, Grade III tumours predominated (59%), consistent with the high-grade nature of basal-like TNBC [3]. CK5/6 expression and the overall basal phenotype did not demonstrate a significant association with tumour grade (p>0.05). In contrast, EGFR expression was proportionally higher in Grade II tumours compared to Grade III tumours, indicating a statistically significant (p=0.04) inverse association with increasing tumour grade. This inverse relationship between EGFR expression and higher tumour grade may indicate underlying biological heterogeneity within TNBC and could have important implications for the development and application of EGFR-targeted therapies [19].

Most TNBCs are high-grade invasive carcinomas of no special type, with the rest comprising medullary and metaplastic carcinomas. This suggests that triple negativity can be present in multiple histological subtypes of breast cancer, carrying significant implications for their underlying mechanisms, clinical behaviour, and outcomes [20].

The TILs serve as a surrogate for the host immune response. In the present study cohort, mild TILs were present in 67.5%, moderate in 27.7%, and dense in 4.8%. Basal marker expression (EGFR, CK5/6, combined) was more frequent in moderate and dense TIL categories, though not reaching statistical significance. Prior studies have shown that immune-rich TNBCs which are often basal-like tend, to exhibit higher TIL counts and better response to neoadjuvant chemotherapy [21,22]. The current study trend aligns with these observations, underscoring the potential value of combining immune profiling with basal marker assessment.

Tumour necrosis was observed in 27.7% of cases and showed a higher frequency of EGFR positivity (37 out of 60) and basal phenotype expression (46 out of 60), although these associations were not statistically significant. Similarly, DCIS was present in 22.9% of tumours and followed a comparable pattern. These findings indicate that features such as necrosis and DCIS may co-exist with basal-like characteristics, suggesting an underlying aggressive tumour biology, as supported by the observations of Botti G et al., [18].

A marker of cellular proliferation (Ki-67), serves as an independent predictor of treatment response and overall prognosis. Thirty-two cases (38.6%) demonstrated a Ki-67 proliferation index >50%, while 51 cases (61.4%) had a Ki-67 index ≤50%. High Ki-67 expression is commonly associated with TNBC, correlating with aggressive tumour behaviour and poorer outcomes. According to Alexandrou S et al., BLBC, a frequent TNBC subtype, is marked by a high mitotic index and elevated proliferative activity, largely driven by disruption of the Retinoblastoma (RB) pathway, which facilitates unchecked cell cycle progression [15,23].

Limitation(s)

The IHC for EGFR and CK5/6 as surrogate markers for identifying the basal-like phenotype in TNBC is inherently limited by inter-observer variability and lack of standardised scoring criteria. Differences in staining intensity, positivity thresholds, and interpretation may impact reproducibility across laboratories. The intratumoural heterogeneity may result in sampling bias, especially when small tissue sections such as core biopsies are used.

CONCLUSION(S)

In the present cohort of TNBCs with basal-like phenotype, EGFR and CK5/6 expression were present in a majority of cases, irrespective of tumour size, grade, necrosis, DCIS, or TIL status. Although most associations did not achieve statistical significance, the consistent expression of basal markers highlights their diagnostic and prognostic utility. This suggests a significant association between EGFR expression and tumour grade, with higher proportional expression in Grade II tumours. These findings support incorporating basal marker assessment into routine IHC profiling for TNBC to refine subtype identification and guide targeted treatment strategies. Treatment options for TNBC remain limited, relying mainly on surgery, radiation, and cytotoxic chemotherapy which primarily helps to manage and delay tumour growth and progression. TILs are central to the mechanism, prediction, and enhancement of immunotherapy responses. Their presence not only informs prognosis but also guides therapeutic strategies, making them a critical biomarker and therapeutic tool in oncology.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pathology, Government Medical College, Ernakulam, Kerala, India.
2. Professor, Department of Clinical Laboratory Services and Translational Research- Oncopathology Division, Malabar Cancer Centre Post Graduate Institute of Oncology Sciences and Research, Thalassery, Kerala, India.
3. Associate Professor, Department of Clinical Laboratory Services and Translational Research- Oncopathology Division, Malabar Cancer Centre Post Graduate Institute of Oncology Sciences and Research, Thalassery, Kerala, India.
4. Assistant Professor, Department of Biostatistics, Malabar Cancer Centre Post Graduate Institute of Oncology Sciences and Research, Thalassery, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sangeetha K Nayanar,
Professor, Department of Clinical Laboratory Services and Translational Research-Oncopathology Division, Malabar Cancer Centre Postgraduate Institute of Oncology Sciences and Research, Thalassery-670103, Kerala, India.
E-mail: sgeetanayanar@yahoo.com

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