Expression of c-Myc in Invasive Breast Carcinoma of No Special Type: A Cross-sectional Study

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ABSTRACT

Introduction: Breast cancer is the most common malignancy among women worldwide, accounting for approximately 30% of all female cancers. It is the second leading cause of cancer-related mortality among women globally, with a median age of 61 years at diagnosis. Aberrant expression of c-Myc leads to genomic instability and tumourigenesis. Cellular Myelocytomatosis Oncogene (c-Myc) regulates the Tumour Microenvironment (TME) and plays a role in angiogenesis and stromal cell proliferation. Its overexpression in Invasive Breast Carcinoma (IBC) is associated with poor prognosis. Targeting c-Myc may offer therapeutic benefits, as its inhibition sensitises breast cancer cells to chemotherapy and radiotherapy. However, its role in diagnosis and treatment of IBC warrants further evaluation.

Aim: To study the expression of c-Myc in Invasive Breast Carcinoma of No Special Type (NST).

Materials and Methods: The present cross-sectional study was conducted at KIMS, Bhubaneswar, Odisha, India, from March 2023 to March 2025, and included 55 histologically confirmed cases of IBC. Immunohistochemistry (IHC) for Oestrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor-2 (HER2/neu), Ki-67, and c-Myc was performed in all cases. c-Myc expression was evaluated, and overexpression was defined as ≥20% of tumour cells showing moderate to strong nuclear staining. The association of c-Myc overexpression with various clinicopathological parameters, including age, laterality, histological grade, Ductal Carcinoma In Situ (DCIS), Lymphovascular Invasion (LVI), Perineural Invasion (PNI), tumour stage, nodal stage, nodal status, ER, PR, HER2/neu status, molecular subtypes, and Ki-67 index, was analysed. Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) version 26. The Pearson's chi-square test was used for categorical variables, and a p-value <0.05 was considered statistically significant.

Results: Out of 55 cases, moderate to strong nuclear staining was observed in 20 cases (36.36%), weak staining in 13 cases (23.63%), and negative staining in 22 cases (40.00%). c-Myc nuclear positivity showed a significant association with the presence of a DCIS component (p=0.026) and with molecular subtypes (p=0.05). c-Myc overexpression also showed statistically significant associations with nodal status (p=0.04) and the presence or absence of DCIS (p=0.046).

Conclusion: c-Myc plays an important role in the progression of breast carcinoma and can be effectively evaluated by IHC. In the present study, c-Myc overexpression showed statistically significant associations with positive nodal status and presence of DCIS components in IBC. Therefore, c-Myc may serve as a prognostic biomarker for predicting clinical outcomes in patients with IBC. Further studies with larger sample sizes are essential to better elucidate the role of the c-Myc pathway. Evaluation of c-Myc overexpression may open new avenues for targeted management of breast carcinoma.

Keywords: Cellular myelocytomatosis oncogene, Immunohistochemistry, Prognostic biomarker

INTRODUCTION

Breast cancer is the most common malignancy among women worldwide, having overtaken lung cancer as the leading cancer in terms of incidence in 2020 [1]. Approximately 300,000 new cases were diagnosed in the United States in 2023, with 43,700 deaths, accounting for nearly 30% of all female cancers [2]. Breast cancer is also the second most common cause of cancer-related mortality among women globally. The median age at diagnosis of IBC is 61 years, with incidence increasing with age [3].

Molecular subtyping of breast carcinoma provides valuable insights into patient stratification, management decisions, and the development of targeted therapies [4]. According to Global Cancer Observatory (GLOBOCAN) 2020 data, IBC accounted for 13.5% of all cancers in India, and 10.6% of cancer-related deaths were attributed to breast cancer [1]. Variations in demographic, anthropometric, and lifestyle factors influence the incidence of IBC across Indian populations, with higher rates reported in North-Eastern states and metropolitan cities [4].

Myc-responsive genes regulate cell cycle progression and apoptosis. Under physiological conditions, c-Myc expression

is transiently upregulated during the Quiescence/Resting stage (G0)/First Growth/Preparation phase (G1) phase transition. Sustained high levels of c-Myc may induce apoptosis by inhibiting the expression of other proliferation-related genes [5]. The Myc gene, located on chromosome 8, is one of the most frequently amplified oncogenes. Aberrant c-Myc expression results in altered cell cycle regulation, genomic instability, and tumourigenesis [6].

Several studies have demonstrated c-Myc overexpression in breast cancer, which is associated with poor prognosis [7-11]. c-Myc remains a critical oncogene with a central role in carcinogenesis. The present study evaluates c-Myc expression as a prognostic biomarker in IBC, with the hypothesis that targeting c-Myc and its downstream pathways may offer promising therapeutic strategies.

Study Objectives:

- To study the expression of c-Myc in IBC of NST
- To assess the association of c-Myc overexpression with various clinicopathological parameters

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Department of Pathology, KIMS, Bhubaneswar, Odisha, India, over a period of two years (March 2023 to March 2025). Ethical approval was obtained from the Institutional Ethics Committee (IEC) (Letter No.: KIIT/KIMS/IEC/1891/2024). The study included 55 cases of IBC. Both prospective and retrospective (archival mastectomy/lumpectomy) specimens were analysed.

Inclusion and exclusion criteria: All histologically confirmed cases of carcinoma breast (NOS type) were included. Non-neoplastic breast tissue was used as control. Inadequately preserved specimens and core biopsy samples were excluded from the study.

Study Procedure

Formalin-Fixed, Paraffin-Embedded (FFPE) tissue sections were stained with Haematoxylin and Eosin (H&E) and examined. Tumour typing and grading were performed according to the World Health Organisation (WHO) Classification of Tumours, 5th edition [12]. Assessment of lymph node status and DCIS components was carried out as per the College of American Pathologists (CAP) protocol 2021 [13].

IHC for c-Myc was performed in all cases using a rabbit monoclonal primary antibody (QR061) obtained from Quartett (Biocyc), Germany, following standard laboratory protocols. c-Myc expression was evaluated based on nuclear staining intensity and the percentage of positive tumour cells, and categorised as moderate/strong, weak, or negative [Table/Fig-1]. Prostate carcinoma tissue served as the positive control.

Intensity of staining			Percentage of positive cells		
Negative	Weak	Moderate/strong	Negative	<20% (Weak positive)	≥20% (Over expression)

[Table/Fig-1]: Grading and scoring criteria of c-Myc nuclear staining.

IBC cases showing ≥20% tumour cells with moderate to strong nuclear staining were considered to demonstrate c-Myc overexpression [7]. The association of c-Myc expression with various clinicopathological parameters was analysed statistically.

Molecular subtyping was performed using ER, PR, HER2/neu, and Ki-67. ER and PR were considered positive when ≥1% of tumour nuclei showed nuclear staining, and HER2/neu scoring was performed according to American Society of Clinical Oncology (ASCO)/CAP guidelines, with Fluorescence In Situ Hybridisation (FISH) used for equivocal cases [8]. Ki-67 was evaluated as the percentage of positively stained tumour cell nuclei in hotspot areas [12].

STATISTICAL ANALYSIS

Statistical analysis was performed to determine the association between c-Myc immunostaining levels and various clinicopathological parameters, including age, tumour site, pathological grade, tumour stage, nodal status, proliferative index, Lymphovascular Invasion (LVI), Perineural Invasion (PNI), and molecular subtype. Data were entered into Microsoft Excel 2016. Statistical analysis was carried out using IBM SPSS version 26. The Pearson's chi-square test was used to assess associations between categorical variables. Results were expressed as mean, percentages, and Standard Deviation (SD). The Mann-Whitney U test, chi-square test, and one-way Analysis of Variance (ANOVA) were applied as appropriate. A p-value <0.05 was considered statistically significant.

RESULTS

The present study aimed to evaluate c-Myc expression in IBC and to assess its association with clinicopathological parameters and molecular subtypes. A total of 55 cases of IBC were included. The majority of patients belonged to the ≥50-year age group (35 cases,

63.63%), with a median age of 53 years (range: 36-81 years). Tumours were almost equally distributed between the breasts, with 28 cases (50.90%) in the left breast and 27 cases (49.09%) in the right breast. Histologically, most tumours were Grade 2 (26 cases, 47.27%). An associated DCIS component was identified in 9 (16.4%) cases. LVI was noted in 27 cases (49.09%), and PNI in 14 cases (25.45%). T2 tumours were the most common (27 cases, 49.09%). Lymph node metastasis was absent in 29 cases (52.72%).

A high proliferative index (Ki-67≥14%) was observed in 49 cases (89.09%). Among molecular subtypes, Luminal B (HER2-negative and HER2-positive) were the most frequent, with 13 cases (23.63%) each.

c-Myc nuclear staining intensity was analysed in all 55 cases using a three-tier scoring system. Representative high-power (X400) IHC images showing moderate/strong and weak nuclear staining are depicted in [Table/Fig-2,3], respectively. Prostate carcinoma tissue served as the positive control, with representative images shown in [Table/Fig-4].
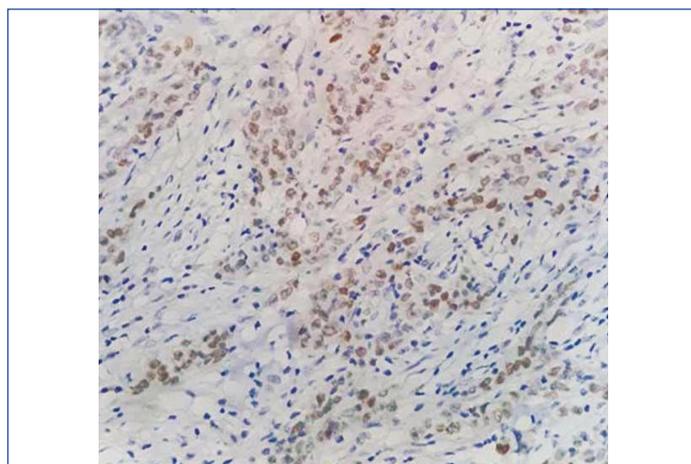
[Table/Fig-2]: Moderate/strong nuclear positivity in tumour cells, c-Myc IHC (X400).
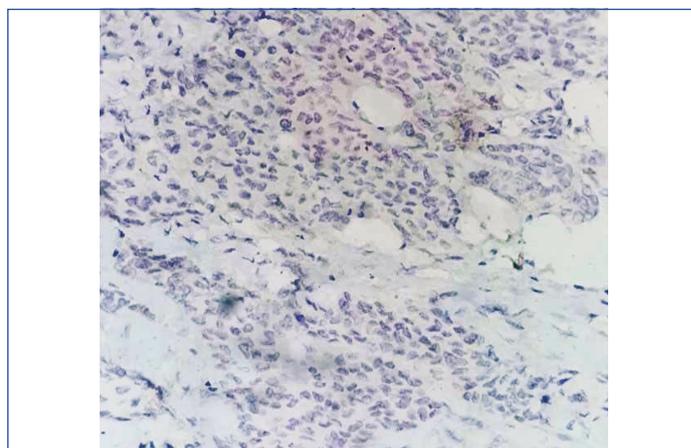
[Table/Fig-3]: Weak nuclear positivity in tumour cells, c-Myc IHC (X400).
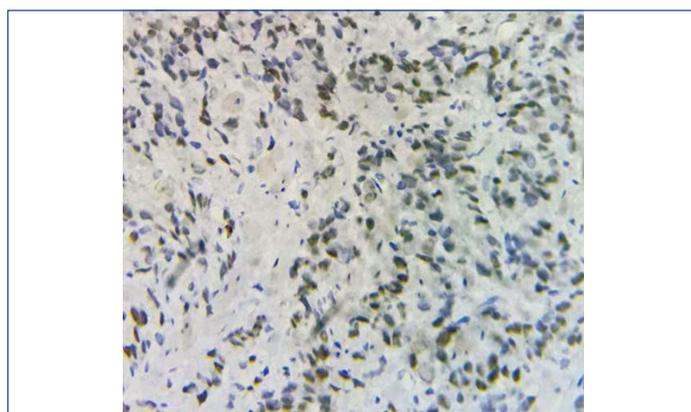
[Table/Fig-4]: Prostatic adenocarcinoma, c-Myc IHC, positive control (X400).

In the present study, moderate to strong c-Myc nuclear staining was observed in 20 cases (36.36%), weak staining in 13 cases (23.63%), and negative staining in 22 cases (40.00%). The association between c-Myc nuclear expression and clinicopathological parameters is summarised in [Table/Fig-5], while c-Myc overexpression (≥20% moderate/strong nuclear staining) is shown in [Table/Fig-6]. Overall, c-Myc overexpression was observed in 27 cases (49.09%) [Table/Fig-7].

A statistically significant association was observed between c-Myc nuclear staining intensity and the presence of a DCIS component

(p=0.026). Among IBC cases with DCIS, 7 (77.77%) cases showed c-Myc overexpression, demonstrating a significant association (p=0.046) [Table/Fig-6].

Molecular subtypes, particularly triple-negative and HER2-enriched tumours, demonstrated stronger c-Myc staining, with a statistically significant association (p=0.05). Additionally, a significant association was observed between c-Myc overexpression and lymph node positivity, with 14 (52.00%) cases showing overexpression (p=0.04) [Table/Fig-6], suggesting a potential link with tumour aggressiveness. No statistically significant association was identified between c-Myc

Parameters		Negative (%)	Weak (%)	Moderate/Strong (%)	No. of case (N=55)	p-value
Age (years)	<50	7 (35.0%)	5 (25%)	8 (40.0%)	20 (36.4%)	0.77
	≥50	15 (43.0%)	8 (22.9%)	12 (34.1%)	35 (63.6%)	
Laterality	Right	12 (44.4%)	7 (25.9%)	8 (29.6%)	27 (49.1%)	0.59
	Left	10 (35.7%)	6 (21.4%)	12 (42.9%)	28 (50.9%)	
Histologic grade	Grade-1	3 (13.6%)	2 (15.3%)	5 (25.0%)	10 (18.2%)	0.46
	Grade-2	11 (50.0%)	6 (46.1%)	9 (45.0%)	26 (47.3%)	
	Grade-3	8 (36.3%)	5 (38.4%)	6 (30.0%)	19 (34.5%)	
DCIS	Absent	21 (95.5%)	11 (84.6%)	14 (70.0%)	46 (83.6%)	0.02*
	Present	1 (4.5%)	2 (15.4%)	6 (30.0%)	9 (16.4%)	
LVI	Absent	11 (50.0%)	8 (61.5%)	9 (45.0%)	28 (50.9%)	0.77
	Present	11 (50.0%)	5 (38.4%)	11 (55.0%)	27 (49.1%)	
PNI	Absent	17 (77.2%)	9 (69.3%)	15 (75.0%)	41 (74.5%)	0.85
	Present	5 (22.7%)	4 (30.7%)	5 (25.0%)	14 (25.5%)	
Tumour stage	T1	8 (36.3%)	5 (38.4%)	4 (20.0%)	17 (30.9%)	0.50
	T2	10 (45.4%)	4 (30.7%)	13 (65.0%)	27 (49.1%)	
	T3	4 (18.2%)	1 (7.7%)	3 (15.0%)	8 (14.5%)	
	T4	0 (0.0%)	3 (23.2%)	0 (0.0%)	3 (5.5%)	
Nodal stage	N0	11(50.0%)	8 (61.5%)	10 (50.0%)	29 (52.7%)	0.84
	N1	6 (27.3%)	3 (23.5%)	7 (35.0%)	16 (29.1%)	
	N2	3 (13.6%)	1 (7.5%)	1 (5.0%)	5 (9.1%)	
	N3	2 (9.1%)	1 (7.5%)	2 (10.0%)	5 (9.1%)	
ER	Positive	14 (63.6%)	8 (61.5%)	13 (65.0%)	35 (63.63%)	0.93
	Negative	8 (36.4%)	5 (38.5%)	7 (35.0%)	20 (36.3%)	
PR	Positive	7 (31.8%)	1 (7.7%)	5 (25.0%)	13 (23.6%)	0.57
	Negative	15 (68.2%)	12 (92.3%)	15 (75.0%)	42 (76.4%)	
Her2/neu	Positive	8 (36.3%)	9 (69.2%)	6 (30.0%)	13 (23.6%)	0.74
	Negative	14 (63.6%)	4 (30.8%)	14 (70.0%)	42 (76.4%)	
Ki-67 index	≥14%	20 (40.8%)	13 (26.5%)	16 (32.7%)	49 (89.1%)	0.18
	<14%	2 (33.3%)	0 (0.0%)	4 (66.7%)	6 (10.9%)	
Molecular sub type	Luminal A	6 (66.7%)	1 (11.1%)	2 (22.2%)	9 (16.4%)	0.05
	Luminal B Her2 Negative	6 (46.2%)	1 (7.7%)	6 (46.2%)	13 (23.6%)	
	Luminal B Her2 Positive	2 (15.4%)	6 (46.2%)	5 (38.5%)	13 (23.6%)	
	Her2 Enriched	6 (60.0%)	3 (30.0%)	1 (10.0%)	10 (18.2%)	
	Triple Negative	2 (20.0%)	2 (20.0%)	6 (60.0%)	10 (18.2%)	

[Table/Fig-5]: c-Myc IHC nuclear expression.
N.B.: *indicates significant p-value (<0.05); DCIS: Ductal carcinoma in situ; LVI: Lymphovascular invasion; PNI: Peri neural invasion; ER: Oestrogen receptor; PR: Progesterone receptor; Statistical test used: Chi-square test, Mann-Whitney U test, One-way ANOVA test

Parameters		c-Myc Negative Cases (%)	c-Myc Positivity <20% Tumour Cells (%)	c-Myc Positivity in ≥20% Tumour Cells(%); Overexpression	Total No. of Cases (N=55)	p-value
Age (years)	<50	7 (35.0%)	2 (10.0%)	11 (55.0%)	20 (36.4%)	0.80
	≥50	15 (43.0%)	4 (11.4%)	16 (45.7%)	35 (63.6%)	
Laterality	Right	12 (44.4%)	3 (11.1%)	12 (44.4%)	27 (49.1%)	0.78
	Left	10 (35.7%)	3 (10.7%)	15 (53.6%)	28 (50.9%)	
Histologic grade	Grade-1	3 (13.6%)	0 (0.0%)	7 (25.9%)	10 (18.2%)	0.48
	Grade-2	11 (50.0%)	4 (66.6%)	11 (40.7%)	26 (47.3%)	
	Grade-3	8 (36.3%)	2 (33.4%)	9 (33.3%)	19 (34.5%)	

DCIS	Absent	21 (95.5%)	5 (83.3%)	20 (74.1%)	46 (83.6%)	0.04*
	Present	1 (4.5%)	1 (16.7%)	7 (25.9%)	9 (16.36%)	
LVI	Absent	11 (50.0%)	3 (50.0%)	14 (51.0%)	28 (50.9%)	0.89
	Present	11 (50.0%)	3 (50.0%)	13 (49.0%)	27 (49.1%)	
PNI	Absent	17 (77.2%)	5 (83.3%)	19 (70.3%)	41 (74.5%)	0.56
	Present	5 (22.7%)	1 (16.7%)	8 (29.7%)	14 (25.4%)	
Tumour stage	T1	8 (36.4%)	2 (33.3%)	7 (26.0%)	17 (30.9%)	0.39
	T2	10 (45.4%)	3 (50.0%)	14 (51.8%)	27 (49.1%)	
	T3	4 (18.2%)	1 (16.6%)	3 (11.1%)	8 (14.5%)	
	T4	0 (0.0%)	0 (0.0%)	3 (11.1%)	3 (5.5%)	
Nodal stage	N0	11 (50.0%)	6 (100.0%)	12 (44.4%)	29 (52.7%)	0.72
	N1	6 (27.2%)	0 (0.0%)	10 (37.0%)	16 (29.1%)	
	N2	3 (13.6%)	0 (0.0%)	2 (7.5%)	5 (9.1%)	
	N3	2 (9.2%)	0 (0.0%)	3 (11.1%)	5 (9.1%)	
Nodal status	Negative	10 (45.0%)	6 (100.0%)	13 (48.0%)	29 (52.72%)	0.04*
	Positive	12 (55.0%)	0 (0.0%)	14 (52.0%)	26 (47.28%)	
ER	Positive	14 (63.6%)	3 (50.0%)	18 (66.6%)	35 (63.6%)	0.79
	Negative	8 (36.4%)	3 (50.0%)	9 (33.4%)	20 (36.4%)	
PR	Positive	7 (38.8%)	0 (0.0%)	6 (22.2%)	13 (23.6%)	0.49
	Negative	15 (68.2%)	6 (100.0%)	21 (77.8%)	42 (76.4%)	
Her2/neu	Positive	8 (36.3%)	5 (83.3%)	10 (37.0%)	23 (41.8%)	0.93
	Negative	14 (63.7%)	1 (16.7%)	17 (63.0%)	32 (58.2%)	
Ki-67 index	≥14%	2 (33.3%)	0 (0.0%)	4 (66.7%)	6 (10.9%)	0.50
	<14%	20 (40.8%)	6 (12.2%)	23 (46.8%)	49 (89.1%)	
Molecular sub type	Luminal A	6 (66.7%)	0 (0.0%)	3 (52.0%)	9 (16.6%)	0.07
	Luminal B Her2 Negative	6 (46.2%)	0 (0.0%)	7 (53.8%)	13 (23.6%)	
	Luminal B Her2 Positive	2 (15.4%)	3 (23.1%)	8 (61.5%)	13 (23.6%)	
	Her2 Enriched	6 (60.0%)	2 (20.0%)	2 (20.0%)	10 (18.2%)	
	Triple Negative	2 (20.0%)	1 (10.0%)	7 (70.0%)	10 (18.2%)	

[Table/Fig-6]: Over expression of c-Myc IHC.
N.B.: * indicates significant p-value (<0.05); DCIS: Ductal carcinoma in situ; LVI: Lymphovascular invasion; PNI: Peri neural invasion; ER: Estrogen receptor; PR: Progesterone receptor; Statistical test used: Chi-square test, Mann-Whitney U test, One-way ANOVA test

	% of tumour cells showing expression	No. of cases (%), N-55
c-Myc Expression	Negative	22 (40.00%)
	<20% expression	6 (10.90%)
	≥20% expression (overexpression)	27 (49.09%)

[Table/Fig-7]: c-Myc IHC.

staining intensity or overexpression and other clinicopathological parameters, including age, tumour laterality, histological grade, PNI, ER status, PR status, HER2 status, and Ki-67 index (p>0.05) [Table/Fig-5,6].

DISCUSSION

Breast cancer has become the leading malignancy among women of reproductive age since 1990 and remains a major cause of cancer-related mortality worldwide [1-5]. IBC exhibits diverse biological behaviour, molecular heterogeneity, and variable malignant potential, posing significant therapeutic challenges. Therefore, clinical, pathological, molecular, and genetic factors must be considered to determine optimal treatment strategies [14].

The present study included 55 cases of Invasive Breast Carcinoma of No Special Type (IBC-NST), with evaluation of c-Myc overexpression by immunohistochemistry and its association with clinicopathological parameters. The median age of 53 years observed in the present study is comparable to that reported by Singhi AD et al., and Aulmann S et al., who reported median ages of 46 and 55 years, respectively [15,16].

Understanding the role of c-Myc across different histological subtypes may provide insights into tumour biology in IBC. The findings of the present study suggest that c-Myc IHC expression may serve as a reliable prognostic marker in IBC, consistent with previous reports [9].

The scoring system for c-Myc overexpression used in this study followed the criteria proposed by Naidu R (2004), wherein ≥20% tumour cells with moderate/strong nuclear staining were considered overexpressed [7]. However, Dueck AC et al., defined MYC overexpression as ≥30% invasive cells with strong (3+) nuclear staining [8], while Singhi AD et al., categorised tumours into low, moderate, and high expression groups based on staining percentage [15].

The role of c-Myc in DCIS progression has been suggested in prior studies. Aulmann S et al., using FISH, demonstrated a significant association between c-Myc amplification and DCIS [16]. Although the present study utilised IHC alone, a similar statistically significant association was observed between c-Myc overexpression and DCIS, supporting a potential role of c-Myc in DCIS biology.

A significant association was also observed between c-Myc expression and molecular subtypes, consistent with studies by Dueck AC et al., and Qu J et al., [8,11]. Furthermore, the association between c-Myc overexpression and lymph node metastasis (p=0.04) suggests its role in tumour aggressiveness, in agreement with findings by Dueck AC et al., Green AR et al., and Cui J et al., [8-10], although this association was not observed by Qu J et al., [11].

No significant association was noted between c-Myc overexpression and age, tumour laterality, LVI, PNI, tumour stage, or Ki-67 index, consistent with previously published studies [10,11].

Limitation(s)

The primary limitation of the present study is the small sample size (55 cases) and the use of IHC alone to assess c-Myc expression. These factors may have limited the statistical significance of associations with certain clinicopathological parameters. Future studies incorporating larger cohorts and MYC gene amplification analysis using FISH are warranted for more robust conclusions.

CONCLUSION(S)

In the present study, c-Myc overexpression demonstrated a statistically significant association with lymph node positivity and the presence of a DCIS component in invasive breast carcinoma. These findings suggest that c-Myc may serve as a prognostic biomarker for predicting disease progression and clinical outcomes in IBC patients. Further large-scale studies are required to elucidate the role of c-Myc-mediated pathways, which may open new avenues for targeted breast cancer management.

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