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Original Research Article

IMMUNOHISTOCHEMICAL EXPRESSION OF ANAPLASTIC LYMPHOMA KINASE (ALK) IN TRIPLE NEGATIVE BREAST CANCER: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Triple negative breast cancer (TNBC) is an aggressive molecular subtype characterised by absence of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, leaving patients without established targeted therapeutic options. Anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase encoded on chromosome 2p23, has been identified as a potential oncogenic driver in several solid tumours. Overexpression of ALK renders tumours susceptible to targeted inhibition with tyrosine kinase inhibitors such as crizotinib, offering a potential therapeutic avenue for TNBC patients. Objective of this study is to evaluate the immunohistochemical expression of ALK in triple negative breast cancer and to correlate ALK expression with clinicopathological parameters including age, tumour size, histological grade, nodal status, lymphovascular invasion, TNM stage, and Ki67 proliferation index. **Materials and Methods**: Sixty formalin-fixed paraffin-embedded tissue blocks of TNBC, retrieved from the Department of Pathology in a tertiary care teaching hospital., were subjected to ALK immunohistochemistry using the OT1A4 clone antibody. Positive staining was defined as cytoplasmic granular/membranous staining at 2+ or 3+ intensity. Chi-square analysis and one-way ANOVA were applied; $p < 0.05$ was considered significant. **Results:** TNBC accounted for 32.7% (71/217) of all breast cancers diagnosed over the two-year study period. Among 60 TNBC cases studied, 25 (41.7%) showed positive ALK immunostaining. The mean Ki67 value was significantly higher in ALK-positive cases (41% vs 28%, $p<0.001$). Lymphovascular invasion ($p=0.017$) and axillary nodal metastasis ($p=0.017$) were significantly associated with ALK positivity. The majority of tumours were grade 3 (83.3%) with a median patient age of 50 years. **Conclusion:** ALK is significantly overexpressed in 41.7% of TNBC cases and is associated with higher proliferative activity, lymphovascular invasion, and nodal metastasis—markers of aggressive biological behaviour. ALK immunohistochemistry is a feasible, cost-effective screening tool in resource-limited settings. Targeted therapy with ALK inhibitors warrants further clinical investigation in ALK-positive TNBC.

INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy among women worldwide and represents a leading cause of cancer-related mortality. According to the World Health Organization, approximately 2.09 million new breast cancer cases and 627,000 deaths were recorded globally in 2018.[1] In India, breast cancer has surpassed cervical cancer as the most common female malignancy, with 87,090 deaths recorded in 2018, the second highest globally.[2] The estimated number of breast cancer cases in India is projected to reach 1,797,900 by 2020, driven by urbanisation, lifestyle changes, and population growth.[3]

Breast carcinoma is a heterogeneous disease encompassing a broad spectrum of morphologically and molecularly distinct subtypes with varying biological behaviour and prognosis. Molecular classification using hormone receptor status and HER2 expression has transformed the clinical management of breast cancer, enabling hormone

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receptor-directed endocrine therapy and HER2-targeted agents. However, triple negative breast cancer (TNBC)—defined by the absence of estrogen receptor (ER), progesterone receptor (PR) expression and lack of HER2 amplification or overexpression—remains without an established targeted therapeutic strategy, and is therefore referred to as an 'orphan disease' in the context of precision oncology.[10]

TNBC constitutes approximately 10–24% of all invasive breast cancers globally; however, data from Indian cohorts consistently document a higher prevalence, estimated between 27–33%.[7,12] TNBC is characterised by younger age at onset, higher histological grade, increased Ki67 proliferative index, propensity for early visceral metastasis, and limited disease-free survival compared to receptor-positive subtypes.[11] The absence of targetable molecular drivers makes TNBC uniquely challenging, necessitating the search for novel biomarkers.

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase first identified in 1994 in association with anaplastic large cell lymphoma.[13] ALK is encoded on chromosome 2p23 and its oncogenic activation—through gene amplification, copy number gain, or chromosomal translocation—drives tumour cell survival via the PI3K/AKT, RAS/MAPK, and JAK/STAT signalling pathways. Fusion proteins derived from ALK translocations produce constitutive tyrosine kinase activation, inhibit apoptosis, and promote uncontrolled cellular proliferation. ALK rearrangements and overexpression have been characterised in non-small cell lung cancer, anaplastic large cell lymphoma, and neuroblastoma, where they serve as validated targets for tyrosine kinase inhibitors including crizotinib, ceritinib, and alectinib.

Emerging evidence suggests that ALK protein overexpression occurs in a clinically significant proportion of TNBC cases. Siraj et al. documented ALK alteration in 46.9% of TNBC specimens in a Saudi Arabian cohort, indicating that ALK may constitute an important oncogenic event in this aggressive subtype.[3] Screening for ALK expression by immunohistochemistry (IHC) is a practical and economical method, particularly in resource-limited government hospital settings where fluorescence in situ hybridisation (FISH) may not be routinely accessible. Identification of ALK-overexpressing TNBC could expand the therapeutic landscape for these patients through use of established ALK inhibitors.

The present study was undertaken to evaluate the immunohistochemical expression of ALK in TNBC cases at a tertiary care government institution in South India, and to investigate its association with clinicopathological parameters. The findings aim to provide evidence supporting ALK IHC as a potential therapeutic biomarker screening tool in TNBC.

Objectives

Primary Objective: To evaluate the immunohistochemical expression of anaplastic lymphoma kinase (ALK) in triple negative breast cancer using the 1A4 clone antibody. Secondary O**bjectives:** To correlate ALK expression with clinicopathological parameters including age, tumour laterality, tumour site, tumour size, histological subtype, Nottingham histological grade, lymphovascular invasion, axillary nodal metastasis, TNM stage, and Ki67 proliferation index; and to compare findings with published literature.

MATERIALS AND METHODS

This was an observational, cross-sectional study conducted over a two-year period in the Department of Pathology at a tertiary care teaching hospital. The study was approved by the Institutional Ethics Committee. A total of 60 formalin-fixed paraffin-embedded (FFPE) tissue blocks of triple negative breast cancer fulfilling inclusion criteria were retrieved from the department archives.

The study comprised 60 cases of triple negative breast cancer diagnosed on histopathological examination and confirmed by immunohistochemical application of ER, PR, HER2, and Ki67 biomarkers. Inclusion criteria were all histologically and immunohistochemically confirmed TNBC cases with adequate archival FFPE material. Exclusion criteria included all other immunohistochemical subtypes of breast malignancy, cases with inadequate tissue, and poorly fixed specimens.

Histopathological Processing

All breast biopsy and excision specimens were fixed in 10% neutral buffered formalin within one hour of removal from the patient, as per College of American Pathologists (CAP) recommended ischemic time guidelines for ER, PR, HER2, and FISH testing. Fixation time was maintained between 8 and 72 hours to ensure optimal immunoreactivity. Tissues were processed through graded alcohols and xylene using an automated histokinette, embedded in paraffin wax, and sectioned at 4–5 micron thickness using a semi-automated microtome. Sections were stained with haematoxylin and eosin (H&E) for morphological assessment. Histological subtyping was performed according to the 2019 WHO Classification of Tumours of the Breast, and grading was carried out using the Nottingham Histological Score (NHS) system, incorporating glandular differentiation, nuclear pleomorphism, and mitotic rate.

Immunohistochemistry – Routine Biomarkers

Routine IHC for ER, PR, HER2/neu, and Ki67 (MIB-1) was performed on all breast carcinoma cases as per standard protocols. TNBC was defined as absence of ER and PR staining and negative HER2 status (score 0 or 1+, or FISH non-amplified for 2+ equivocal cases). Ki67 percentage was calculated by counting a minimum of 500 tumour cell nuclei at high-power fields and expressed as the percentage of positively staining cells. TNM staging was performed in accordance with AJCC (8th edition) guidelines.

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ALK Immunohistochemistry

ALK IHC was performed on representative FFPE TNBC blocks using the OT1A4 clone ALK/CD246 antibody (PathnSitu, India) following manufacturer guidelines. Sections of 4–5 µm thickness were cut onto positively charged slides. The HRP polymer detection technique was employed as follows: overnight incubation at 37°C followed by slide warmer treatment at 70°C for 30 minutes; deparaffinisation in two changes of xylene (10 minutes each); hydration through graded alcohols; antigen retrieval by pressure cooker in TRIS-EDTA buffer (pH 8.5–9.0) at 160°C for three whistles; endogenous peroxidase blocking with 3% H_2 O_2 for 10 minutes; primary antibody (ALK 1A4) application for 45 minutes; secondary antibody with horseradish peroxidase for 10 minutes; DAB chromogen development for 5 minutes; and counterstaining with haematoxylin. An ALK-positive inflammatory myofibroblastic tumour block served as positive control.

ALK immunostaining was evaluated by examining cytoplasmic staining at high-power fields (40×). The 1A4 clone intensity scoring system was applied as follows: 0 = no staining (negative); 1+ = weak staining (equivocal/negative); 2+ = moderate cytoplasmic staining (positive); 3+ = strong cytoplasmic staining (positive). Cases showing 2+ or 3+ granular cytoplasmic or membranous positivity were classified as ALK-positive. Cases with diffuse weak (1+) cytoplasmic staining and those with no staining were classified as ALK-negative [14,15].

Statistical Analysis

Data were entered and analysed using IBM SPSS Statistics version 25. Descriptive statistics including frequency and percentage were computed for all categorical variables. Chi-square test was used to assess associations between ALK immunostaining and clinicopathological variables. One-way ANOVA was employed to compare mean Ki67 values between ALK-positive and ALK-negative groups. A p-value of <0.05 was considered statistically significant.

RESULTS

During the study period, a total of 217 breast cancer cases were diagnosed by histopathological examination and immunohistochemistry at tertiary care teaching hospital. Of these, 71 cases (32.7%) were classified as triple negative breast cancer. Sixty suitable FFPE blocks were retrieved from the archives for ALK IHC study. [Table 1 and Table 4]

Table 1: Clinicopathological profile of the TNBC study population (N=60)

Clinicopathological Parameter	Frequency (n=60)	Percentage (%)
Age group (41–50 years)	24	40.0
Age group (30–40 years)	10	16.6
Age group (51–60 years)	20	33.4
Age group (>60 years)	6	10.0
Right breast (laterality)	31	51.7
Upper outer quadrant (tumor site)	20	33.3
Tumor size >5 cm (Group C)	32	53.3
Tumor size 2–5 cm (Group B)	27	45.0
Histological Grade 3	50	83.3
Infiltrating Ductal Carcinoma (IDC)	54	90.0
Nodal metastasis (N1)	9	15.0
Lymphovascular invasion	9	15.0
Ki67 >20%	56	93.3
pT3 stage	32	53.3

The age of patients in the study population ranged from 34 to 72 years, with a mean and median age of 50 years (SD ±9.03). The most commonly affected age group was 41–50 years (n=24, 40%), followed by 51–60 years (n=20, 33.4%). Ten patients (16.6%) were younger than 40 years, indicating a significant proportion of younger women affected by TNBC. Regarding tumour laterality, 31 cases (51.7%) involved the right breast and 29 cases (48.3%) involved the left breast. The upper outer quadrant was the most common tumour site, accounting for 20 cases (33.3%), followed by the lower inner quadrant (23.3%).

The majority of tumours (32 cases, 53.3%) presented with a size exceeding 5 cm (Group C), while 27 cases (45.0%) measured between 2–5 cm (Group B). Only one case presented with a tumour less than 2 cm. Infiltrating ductal carcinoma NOS was the predominant histological subtype (54 cases, 90%), with metaplastic carcinoma (4 cases, 6.7%) and medullary carcinoma (2 cases, 3.3%) constituting the remainder. Histological grading using the Nottingham scoring system revealed that 83.3% of cases (n=50) were grade 3, while 16.7% (n=10) were grade 2; no grade 1 cases were observed, underscoring the aggressive phenotype of TNBC. Lymphovascular invasion was identified in 9 cases (15%), all of which also showed axillary nodal metastasis (N1 stage, 15%). Regarding TNM staging, 32 cases (53.3%) were pT3, 27 cases (45.0%) were pT2, and one case was pT1.

The Ki67 proliferation index was elevated (>20%) in 56 of 60 cases (93.3%), reflecting the characteristically high mitotic activity of TNBC. The mean Ki67 value for the entire study population was 33.43% (range 16–78%). Only four cases had Ki67 values below 20%, consistent with published

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observations that TNBC typically displays high-grade proliferative characteristics.

ALK immunohistochemistry was applied to all 60 TNBC blocks. Twenty-five cases (41.7%) demonstrated positive cytoplasmic ALK staining at 2+ or 3+ intensity (Table 2). Among positive cases, 19 (31.7%) showed moderate 2+ intensity and 6 (10.0%) showed strong 3+ intensity. In the ALK-negative group (n=35, 58.3%), 16 cases showed weak diffuse cytoplasmic staining (1+), and 19 cases demonstrated no staining. All positive cases showed granular cytoplasmic staining, consistent with the expected pattern for cytoplasmic ALK expression using the 1A4 clone antibody.

Table 2: Distribution of ALK immunostaining in TNBC study population (N=60)

ALK Staining	Frequency (n=60)	Percentage (%)
Positive (2+ or 3+ intensity)	25	41.7
Negative (weak/no staining)	35	58.3
Strong (3+) intensity among positive	6	10.0
Moderate (2+) intensity among positive	19	31.7
Weak (1+) diffuse cytoplasmic	16	26.7
No staining	19	31.7

Correlation of ALK Expression with Clinicopathological Parameters

Correlation of ALK immunostaining with clinicopathological variables is presented in Table 3. Lymphovascular invasion was significantly associated with ALK positivity, with 7 of 25 ALK-positive cases (28%) demonstrating LVI compared to only 2 of 35 ALK-negative cases (5.7%) (χ^2=5.681, p=0.017). Similarly, axillary nodal metastasis (N1 stage) was significantly more frequent in ALK-positive cases (7 of 25, 28.0%) than in ALK-negative cases (2 of 35, 5.7%) (χ^2=5.681, p=0.017). Although ALK-positive tumours showed a trend towards larger tumour size, with 68% of positive cases presenting as Group C (>5 cm) versus 42.9% in the negative group, this difference did not reach statistical significance (χ^2=5.821, p=0.055). Age, laterality, tumour site, histological subtype, and histological grade showed no statistically significant association with ALK staining status. Regarding TNM stage, pT3N1 staging was observed in 7 of 25 ALK-positive cases (28.0%) compared to 2 of 35 ALK-negative cases (5.7%), though the overall chi-square analysis did not reach significance (χ^2=7.585, p=0.55).

The mean Ki67 value was significantly higher in ALK-positive cases (41.0%, ±14.24) compared to ALK-negative cases (28.03%, ±9.70), with a highly significant p-value of <0.001 on one-way ANOVA analysis. This strong association between high proliferative index and ALK positivity is among the most important findings of this study and supports the oncogenic relevance of ALK activation in TNBC.

Table 3: Correlation of ALK immunostaining with clinicopathological parameters

Parameter	ALK Positive n(%)	ALK Negative n(%)	Chi-square	p-value
Lymphovascular invasion (present)	7 (28.0%)	2 (5.7%)	5.681	0.017*
Nodal metastasis (N1)	7 (28.0%)	2 (5.7%)	5.681	0.017*
Tumor size >5 cm	17 (68.0%)	15 (42.9%)	5.821	0.055
Histological Grade 3	22 (88.0%)	28 (80.0%)	0.672	0.412
IDC subtype	22 (88.0%)	32 (91.4%)	3.276	0.194
pT3N1 stage	7 (28.0%)	2 (5.7%)	7.585	0.55
Ki67 mean (±SD)	41.0 (±14.24)	28.03 (±9.70)	—	<0.001*
Age 41–60 years (combined)	20 (80.0%)	24 (68.6%)	2.126	0.547

Statistically significant (p < 0.05)

DISCUSSION

This study evaluated the immunohistochemical expression of ALK in 60 TNBC cases at a tertiary care government hospital in South India, representing one of the few such studies from the Indian subcontinent. The findings demonstrate a clinically relevant rate of ALK overexpression (41.7%) with significant associations with markers of aggressive tumour biology.

The observed prevalence of TNBC (32.7%) in our series is notably higher than that reported in Western studies, which generally document rates of 12–18%,[4,5] but is consistent with data from Indian institutions. Kulkarni et al. in a meta-analysis of Indian TNBC data reported a prevalence range of 24–31%,[7] while Pandit et al. documented 26% in a Mumbai cohort.[6] Our finding of 32.7% aligns with reports from other South Indian centres and reinforces the concept of a higher TNBC burden in the Indian population, possibly attributable to genetic predisposition, younger mean age at diagnosis, hormonal factors, and delayed clinical presentation (Table 4).[7,12]

Table 4: Comparison of TNBC prevalence with published Indian and international studies

Study	Total Cases	TNBC Cases	Prevalence (%)
Siraj et al. [3]	972	147	15.0
Al-thoubaity [4]	740	118	16.0
Rakha et al. [5]	1944	318	16.4

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Pandit et al. [6]	2062	536	26.0
Kulkarni et al. [7]	20,000	5400	27.0
Present Study	217	71	32.7

The median age of 50 years in our study is consistent with prior reports from Indian cohorts. Lakshmaiah et al. documented a median age of 44.5 years and Chintalapani et al. reported 50 years in comparable southern Indian populations.[16,17] The younger age of onset of TNBC in India, compared to Western populations where peak incidence typically occurs in the sixth and seventh decades, may reflect differences in reproductive history, BRCA1 germline mutation prevalence, and metabolic profiles. In our series, 57% of patients were 30–50 years of age, emphasising the reproductive-age burden of this disease.

The predominance of large tumours (>2 cm in 98.3% of cases) and high histological grade 3 tumours (83.3%) mirrors findings in several published series. Tzikas et al. reported 80% grade 3 tumours in a European TNBC cohort of 524 patients,[8] while Chintalapani et al. documented 71.7% in 198 Indian patients.[17] The present study's high proportion of grade 3 tumours (83%) suggests a particularly aggressive tumour phenotype, possibly exacerbated by the delayed presentation that characterises breast cancer in lower-middle-income settings.[3,18] Lymphovascular invasion and nodal metastasis, both documented in 15% of cases, are important prognostic indicators that were significantly associated with ALK positivity in this study.

The Ki67 proliferation index exceeded 20% in 93.3% of cases, consistent with the known high proliferative capacity of TNBC. Zhu et al. reported >20% Ki67 in 84.39% of 1800 TNBC cases, and Pan et al. documented 82.8% in their 156-case series.[19,20] The higher proportion in our study may reflect enrichment of clinically advanced cases in a tertiary care government setting. The strong correlation between high Ki67 and ALK positivity ($p<0.001$) is a novel and clinically relevant finding, suggesting that ALK-driven oncogenic signalling may contribute to cell cycle dysregulation and enhanced tumour proliferation in TNBC.

ALK Expression in TNBC

The principal finding of this study is that ALK is overexpressed in 41.7% of TNBC cases, corroborating the landmark study by Siraj et al. which reported ALK alteration in 46.9% of 147 TNBC specimens using a combination of IHC and FISH in a Saudi Arabian cohort.[3] ALK overexpression in TNBC may arise through mechanisms other than classical chromosomal translocations, including gene amplification, increased copy number, activating mutations, or aberrant transcriptional upregulation. In NSCLC, ALK overexpression detected by IHC with the 1A4 clone has demonstrated high concordance with ALK gene rearrangement on FISH, validating IHC as an effective screening platform.[15,21]

The 1A4 clone antibody used in this study produces weaker background staining relative to the D5F3/Ventana assay, which uses a signal amplification system with higher background. With the 1A4 clone, a 2+ or 3+ moderate-to-strong cytoplasmic staining intensity is considered positive, while diffuse weak 1+ staining is classified as negative.[14] Application of this validated scoring system in the present study provides comparable and reproducible results. The granular cytoplasmic pattern of ALK staining observed in positive cases is consistent with previously described IHC patterns in ALK-expressing solid tumours.

The significant association of ALK positivity with lymphovascular invasion ($p=0.017$) and nodal metastasis ($p=0.017$), combined with the markedly higher mean Ki67 in ALK-positive cases (41% vs 28%, $p<0.001$), collectively suggest that ALK expression is associated with a more aggressive tumour phenotype within the already aggressive TNBC subgroup. These findings are clinically relevant because they identify a subset of TNBC patients at particularly high risk of relapse and metastasis who may potentially benefit most from ALK-targeted therapy.

The potential therapeutic implications of ALK overexpression in TNBC are substantial. Crizotinib, a first-generation ALK/MET/ROS1 inhibitor approved for ALK-rearranged NSCLC, has demonstrated activity in other ALK-expressing tumours and is being investigated in solid tumours beyond lung cancer.[10,13] Second-generation inhibitors (ceritinib, alectinib, brigatinib) and third-generation agents (lorlatinib) with enhanced potency and CNS penetration offer further therapeutic options that could be explored in clinical trials targeting ALK-positive TNBC. The absence of effective targeted therapy for TNBC underscores the urgency of identifying and validating biomarkers such as ALK.

Importantly, the feasibility of ALK IHC as a screening tool in resource-limited government hospital settings—using a relatively inexpensive antibody on standard FFPE material—makes implementation practical without requiring the technical expertise and cost associated with FISH. A positive IHC screen would then prompt confirmatory FISH analysis to characterise the specific genomic alteration. This two-step approach is consistent with the ALK testing paradigm established in lung cancer pathology practice.[15,21]

The molecular heterogeneity of TNBC remains a fundamental challenge. While TNBC is broadly classified by the Lehmann transcriptomic schema into six subtypes—basal-like 1, basal-like 2, immunomodulatory, mesenchymal, mesenchymal stem-like, and luminal androgen receptor—ALK

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expression does not appear to segregate to a single subtype. Future studies integrating transcriptomic profiling with ALK IHC and FISH data will be essential for defining the precise molecular context in which ALK activation drives TNBC oncogenesis.[10,18]

Table 5: Comparison of ALK expression in TNBC across published studies

Study	TNBC Cases (n)	ALK Positive (n)	ALK Positivity (%)
Siraj et al. [3]	147	69	46.9
Tzikas et al. [8]	524	~105 (est.)	~20.0
Present Study	60	25	41.6

CONCLUSION

This cross-sectional study demonstrates that ALK is overexpressed in 41.7% of triple negative breast cancer cases as detected by immunohistochemistry using the OT1A4 clone. ALK positivity is significantly associated with lymphovascular invasion, axillary nodal metastasis, and elevated Ki67 proliferation index—all markers of biologically aggressive disease. The high prevalence of TNBC (32.7%) observed in this South Indian tertiary care cohort reinforces the disproportionate burden of this subtype in the Indian population.

The findings support the hypothesis that ALK may play an oncogenic role in TNBC tumorigenesis and provide a rational basis for investigating ALK-targeted therapy in ALK-positive TNBC patients. ALK immunohistochemistry offers a practical, cost-effective screening modality that can be implemented in government hospital settings to identify candidates for ALK inhibitor therapy. However, confirmatory FISH analysis to characterise the underlying genomic alteration is recommended prior to therapeutic decision-making.

The primary limitation of this study is the relatively small sample size (n=60). Larger prospective multicentre studies are warranted to validate the prevalence of ALK overexpression in TNBC, elucidate its precise pathogenetic role, and evaluate the clinical efficacy of ALK inhibitors (e.g., crizotinib, alectinib) in this molecular subset. With continued advancement in TNBC molecular stratification, the unmet therapeutic need of these patients may be addressed through ALK-targeted precision oncology.

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