Vimentin Expression in Infiltrating Ductal Carcinoma NOS of Breast and its Association with Clinicopathological Characteristics

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Abstract

Background: Despite advances in therapy, breast cancer remains the leading cause of cancer related deaths among women worldwide. The most common invasive subtype, Infiltrating Ductal Carcinoma (IDC), often presents at advanced stages.

Rapid progression and therapeutic resistance contribute to such poor outcomes. Vimentin, a cytoskeletal protein linked to epithelial-mesenchymal transition (EMT), is associated with aggressive tumor behavior, poor prognosis, and drug resistance, making it a potential prognostic and predictive marker for IDC.

Objectives: To evaluate vimentin expression in IDC-NOS of the breast and its association with clinicopathological features.

Methods: This cross-sectional observational study was conducted in the Department of Pathology, Dhaka Medical College, from September 2022 to August 2024. Sixty histopathologically diagnosed IDC-NOS cases were examined. Immunohistochemistry for vimentin was performed on formalin-fixed, paraffin-embedded tissues at AI Khan Lab Ltd., Dhaka. Associations with clinicopathological features were analyzed; $p < 0.05$ was considered statistically significant.

Results: Vimentin expression was positive in 43.3% of cases. It was significantly higher in Grade 3 tumors (65.4%, $p < 0.001$) and in the triple-negative subtype (57.7%, $p = 0.003$). No significant association was observed with age, tumor size, stage, or lymphovascular invasion.

Conclusion*:* Vimentin expression showed significant associations with aggressive breast cancer phenotypes, particularly higher grade and TNBC subtype. These findings suggest that vimentin may serve as a useful supplementary prognostic marker to aid in risk stratification and management of breast cancer.

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Introduction

Breast cancer (BC) is the most frequently diagnosed malignancy and the leading cause of cancer-related mortality in women worldwide.[1] In 2020, over 2.3 million new cases were reported globally, with projections exceeding 3 million annually by 2040.[2] Rapid progression and chemoresistance contribute to the majority of these cancer-related mortalities.[3] Thus, targeting factors that are involved in this mechanism can provide milestone progress in field of breast cancer therapy.[4]

Many studies suggest that neoplastic epithelial cells that have lost their epithelial morphology and acquire mesenchymal characteristics, termed as Epithelial mesenchymal transition (EMT), related with invasiveness and metastatic potential of tumor.[5,6,7] In breast cancer, EMT activation not only enhances metastasis, but also increases proliferation of tumor cells, and these events lead to treatment resistance.[4] Vimentin, an intermediate filament protein normally expressed in mesenchymal cells, is a hallmark of EMT and a regulator of cell motility.[8] During oncogenic transformation of epithelial cells in cancers, vimentin expression increases as cells undergo EMT, reflecting heightened cell motility and invasiveness.[9] Elevated vimentin levels are linked to aggressive tumor phenotypes and poor prognosis, making it a potential therapeutic target to inhibit EMT and metastasis.[10]

Several studies suggest that the expression of vimentin in breast cancer is an important prognostic indicator.[11,12] It's expression is significantly associated with high grade infiltrating ductal carcinomas, low estrogen receptor (ER), low progesterone receptor (PR), advanced stages of breast cancer and metastasis.[13,14] In addition, high vimentin expression is often found in cancer stem cells, contributing to tumor initiation and therapeutic resistance, which ultimately leads to reduced survival in breast cancers patients, particularly in triple-negative cases.[10,15] Thus, assessing vimentin expression can be a great help in stratifying the patients with breast carcinoma for personalized treatment approaches.[11]

Infiltrating ductal carcinoma (IDC), which accounts for up to 75% of invasive breast carcinomas, is a heterogeneous disease with a wide range of clinicopathological characteristics.[16] These features such as tumor size, histological grade, lymph node status, and molecular markers, guide the choice of therapy and help in determining the prognosis of the patient.[17] Thereby, studying the association between vimentin expression and clinicopathological characteristics can shed light on the unique features of breast cancer in our country and may assist in developing targeted interventions and personalized treatment plans for the patients.

Methods

This cross-sectional observational study was conducted from September 2022 to August 2024. Histopathological evaluation was carried out in the Department of Pathology, Dhaka Medical College, and immunohistochemistry was performed at AI Khan Lab Ltd, Dhaka. The study included 60 female patients, irrespective of age, diagnosed with infiltrating ductal carcinoma (NOS) of the breast from modified radical mastectomy specimens. Samples were selected using purposive sampling. Cases with a prior history of neoadjuvant chemotherapy or radiotherapy and recurrent breast carcinoma were excluded.

The Institutional Review Board (IRB) of Dhaka Medical College provided ethical clearance prior to commencement of this study. Informed written consent was taken

from patient or patient's legal guardian in each case with assurance of confidentiality. Demographic data, such as age, associated other clinical history and immunohistochemical reports of hormone receptors (ER, PR) and HER2/neu receptor status were obtained and recorded. Tumor size on gross examination was documented. Hematoxylin and eosin (H&E) stained sections were examined thoroughly to evaluate histopathological grade, stage, lymphovascular invasion and regional lymph nodal involvement by the tumor. Tumor grading was performed according to the Nottingham modification of the Bloom Richardson grading system. The staging of the tumors was done following TNM classification of breast carcinoma, according to American Joint Committee on Cancer (AJCC). Luminal, HER2-enriched, and TNBC molecular subtypes were determined for each case by evaluating the immunohistochemical reports of ER, PR, and HER2 receptors.

Immunohistochemical evaluation of Vimentin: Paraffin-embedded tumor blocks were sectioned at 4 µm and mounted on poly-L-lysine–coated slides. Sections were immunostained with FLEX Monoclonal Mouse Anti-Vimentin, Clone V9, Ready to use (Link), Dako Denmark.

Vimentin-stained slides were examined, and the most representative tumor areas were selected for scoring the vimentin expression using light microscopy. Tissue section of tonsil was taken as positive control. A cut-off of 10% tumor cells showing cytoplasmic granular brown staining was considered as positive expression of Vimentin.[18]

Immunohistochemical scoring of vimentin expression[18]

Score 0:	<10% or no staining of tumor cells.
Score 1:	Weak staining of more than or equal 10% of tumor cells.
Score 2:	Moderate staining of more than or equal 10% of tumor cells.
Score 3:	Strong staining of more than or equal 10% of tumor cells.

For statistical analysis, scores were divided into two groups:[18]

- Positive: Score 1, Score 2 and Score 3
- Negative: Score 0

Statistical analysis and result: A data collection sheet was prepared, incorporating patient information, investigation reports, and analysis was conducted using appropriate statistical tests. Descriptive analysis included frequency distribution, mean, median, and standard deviation as required. Means and standard deviation for continuous variables and frequency distributions for categorical variables were used to describe the characteristics of the total sample. The association between variables was assessed by performing the Chi-square test and Fisher's exact test. Statistical significance was set at $p < 0.05$.

Results

In the current study among the 60 infiltrating ductal carcinoma (IDC) cases studied, vimentin was positive in 26 (43.33%) cases while 34 (56.67%) cases were negative.

Table I: Distribution of the study cases according to vimentin expression (n=60)

Vimentin Score	Frequency	Percentage
Score 0	34	56.7
Score 1	6	10.0
Score 2	14	23.3
Score 3	6	10.0
Vimentin expression		
Positive	26	43.3
Negative	34	56.7

Table II shows the association of vimentin expression with age of the study cases. Fisher's Exact test yields there was no statistically significant association (p = 0.634).

Table II: Association of vimentin expression with age of the study cases (n=60)

Age groups	Vimentin expression		p value
	Positive (n=26)	Negative (n=34)	
26-35 years	6 (23.1)	6 (17.6)	
36-45 years	8 (30.8)	10 (29.4)	
46-55 years	10 (38.5)	10 (29.4)	0.634[a]
56-65 years	2 (7.7)	6 (17.6)	
>=66 years	0 (0.0)	2 (5.9)	

[a] Fisher's exact test

A significant association was found between vimentin expression and both histological grade ($p<0.001$) and molecular subtypes ($p<0.003$) (Table III). Positive vimentin expression increased with higher histological grades. Among the study cases, TNBC subtype (57.7%) shows significantly higher positive vimentin expression compared to Luminal (30.8%) and HER2 enriched (11.5%) subtypes.

Table III: Association of vimentin expression with histological grade and molecular subtypes (n=60)

Variables	Vimentin expression		p value
Histological grade	Positive (n=26)	Negative (n=34)	
Grade 1	0 (0.0)	7 (20.6)	
Grade 2	9 (34.6)	22 (64.7)	<0.001[a]
Grade 3	17 (65.4)	5 (14.7)	
Molecular subtype			
Luminal	8 (30.8)	24 (70.6)	
TNBC	15 (57.7)	6 (17.6)	0.003 [a]
Her2 enriched	3 (11.5)	4 (11.8)	

[a] Fisher's exact test

Vimentin expression did not significantly vary with pathological T (p = 0.964) and N stage (p = 0.334) and lymphovascular invasion (p = 0.407) (Table IV).

Table IV: Association of vimentin expression with pathological T and N stage, and LVI (n=60)

Variables	Vimentin expression		p value
Pathological T Stage	Positive (n=26)	Negative (n=34)	
pT1	5 (19.2)	5 (14.7)	0.964[a]
pT2	17 (65.4)	24 (70.6)	
pT3	2 (7.7)	3 (8.8)	
pT4	2 (7.7)	2 (5.9)	
Pathological N Stage			
N0	13 (50.0)	13 (38.2)	0.334[a]
N1	8 (30.8)	7 (20.6)	
N2	3 (11.5)	10 (29.4)	
N3	2 (7.7)	4 (11.8)	
LVI			
Not identified	18 (69.2)	20 (58.8)	0.407 [b]
Present	8 (30.8)	14 (41.2)	

[a] Fisher's exact test
[b] Chi square test

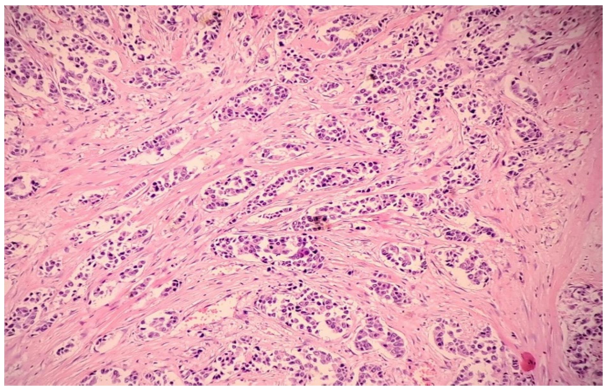

Figure 1. H & E-stained section of Grade-1 Infiltrating Ductal Carcinoma

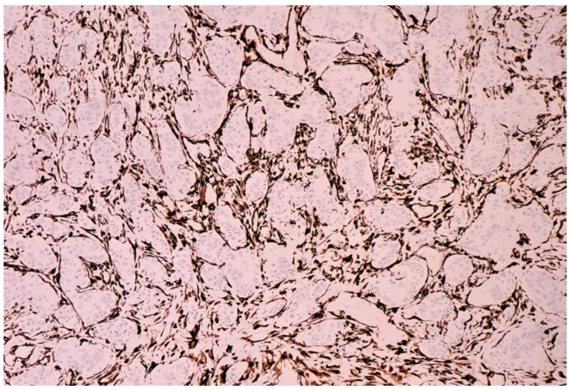

Figure 2. Microscopic picture of negative Vimentin expression in Grade-1 Infiltrating Ductal Carcinoma

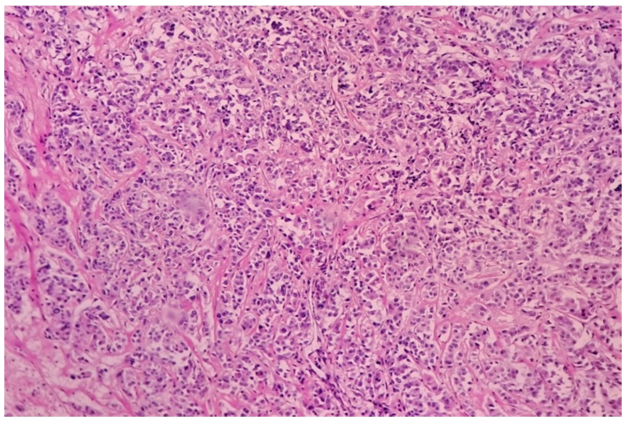

Figure 3. H & E-stained section of Grade-2 Infiltrating Ductal carcinoma

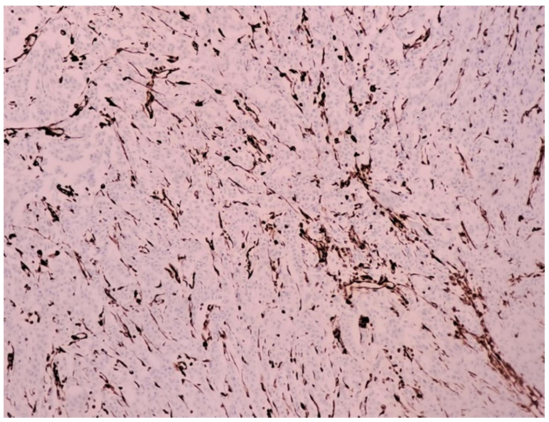

Figure 4. Microscopic picture of negative Vimentin expression in Grade-2 Infiltrating Ductal Carcinoma

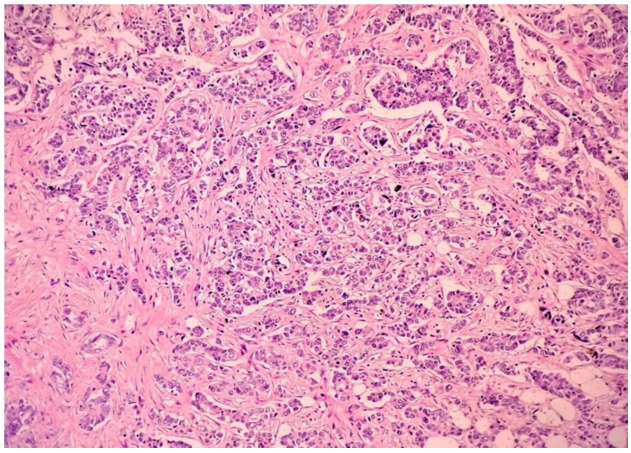

Figure 5: H & E-stained section of Grade-2 Infiltrating Ductal carcinoma

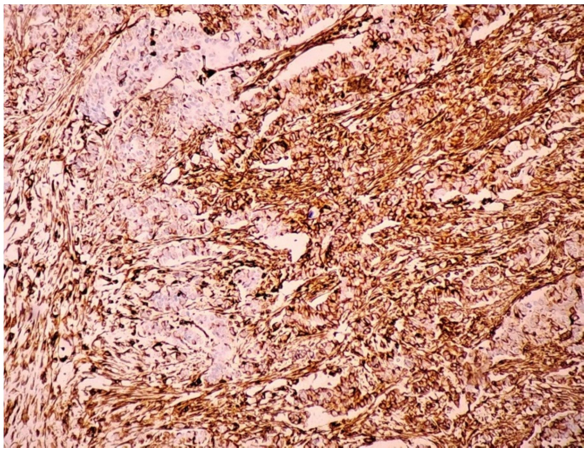

Figure 6: Microscopic picture of strong Vimentin positivity in Grade-2 Infiltrating Ductal Carcinoma

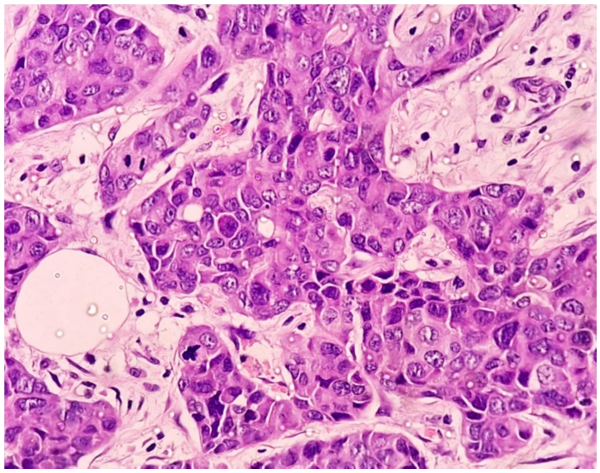

Figure 7. H & E-stained section of Grade-3 Infiltrating Ductal Carcinoma

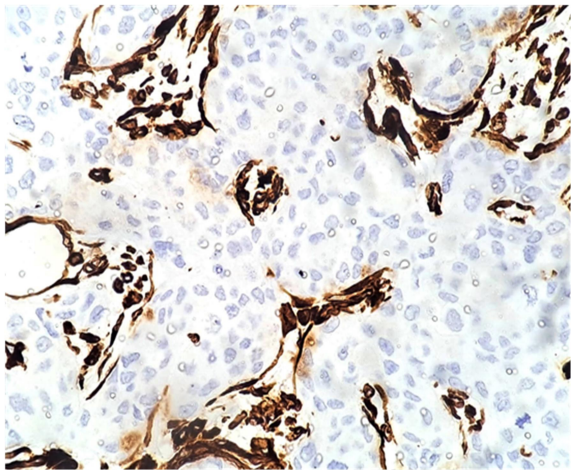

Figure 8. Microscopic picture of negative Vimentin expression in Grade-3 Infiltrating Ductal Carcinoma

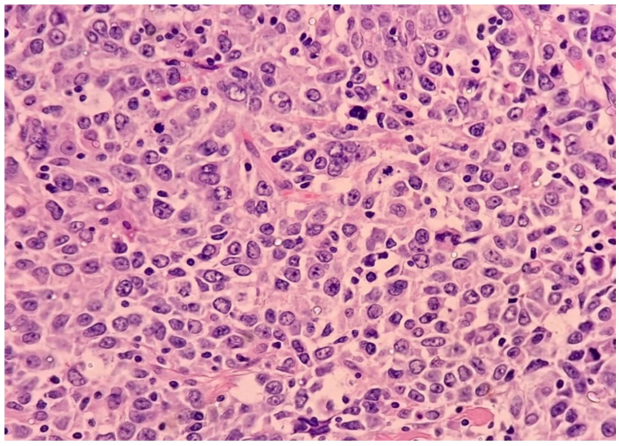

Figure 9. H & E-stained section of Grade-3 Infiltrating Ductal carcinoma

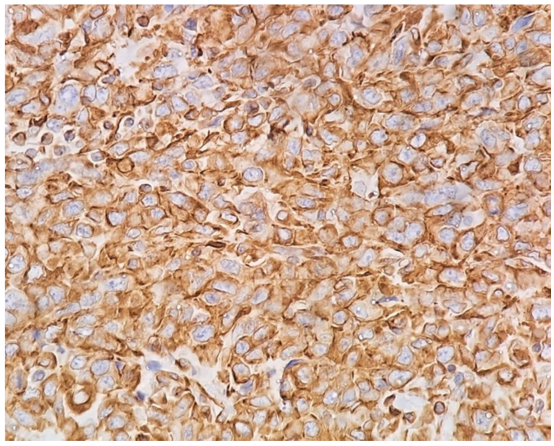

Figure 10. Microscopic picture of moderate Vimentin positivity in Grade-3 Infiltrating Ductal Carcinoma

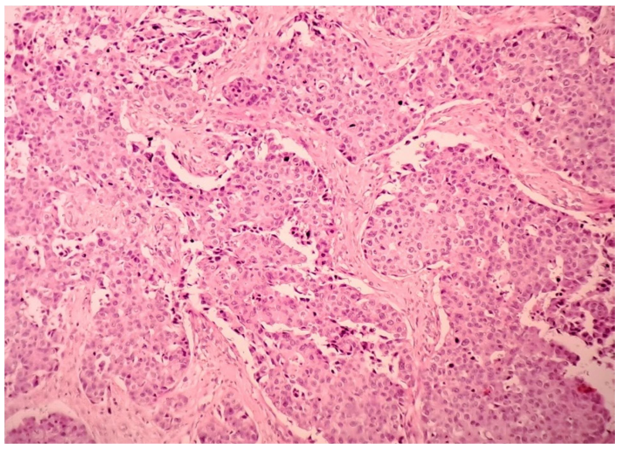

Figure 11. H & E-stained section of Grade-3 Infiltrating Ductal carcinoma

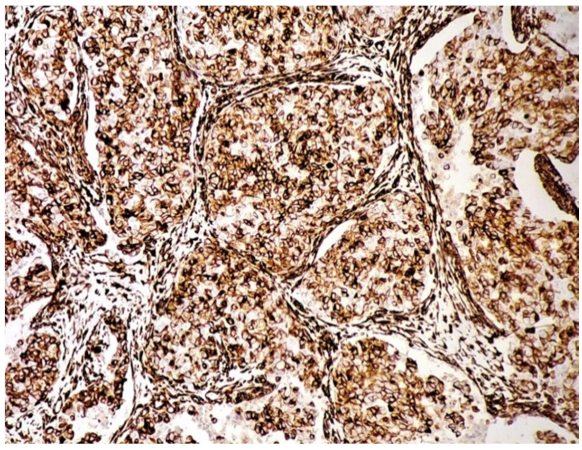

Figure 12. Microscopic picture of strong Vimentin positivity in Grade-3 Infiltrating Ductal Carcinoma

Discussion

Evaluation of the immunohistochemical expression of Vimentin was done in the sixty cases of infiltrating ductal carcinoma NOS of breast. Positive vimentin expression was observed in 43.33% cases while negative expression 56.67% cases. It revealed variability compared to other studies where reported percentages ranged from 18% to 75.7%.[19-24] The observed differences in vimentin expression across studies may be attributed to variations in methodologies and scoring system used for assessing vimentin positivity.

The current study found that positive vimentin expression was highest in the 46-55 years age group (38.5%) and lowest in the ≥66 years age group (0%). However, the differences in our study were not statistically significant (p = 0.634), similar to Sharma et al.[23] who found no significant association between vimentin expression and age.

Considering histological grading of breast carcinoma according to Nottingham modification of Bloom Richardson system, the present study showed that positive vimentin expression was increased with higher histologic grades, being 0% in Grade 1 tumors, 34.6% in Grade 2, and 65.4% in Grade 3 tumors. Negative vimentin expression was most prevalent in Grade 2 tumors (64.7%), followed by Grade 1 (20.6%) and Grade 3 (14.7%) tumors. The difference in vimentin expression across histologic grades was statistically significant (p < 0.001). This finding coincides with the observations of Sharma et al.[8], Vani[18] and Kusinska et al.[22]. In a study conducted in India also reported that vimentin expression associated with high tumor grade in breast carcinoma.[20] In contrast, Vora et al.[24] reported no statistically significant association between vimentin expression and histologic grades.

In our study, Vimentin expression did not significantly vary with tumor size (p = 0.923), lymphovascular invasion (p = 0.407), pT (p = 0.964) and pN stage (p = 0.334). In this study, positive vimentin expression was observed in 30.8% of cases with lymphovascular invasion (LVI), though this difference was not statistically significant. This contrasts with Sharma et al.[8] and Khillare et al.[21] who reported statistically significant association between vimentin expression and LVI. The discrepancy in findings may be attributed to differences in study design or sample characteristics.

The present study showed that positive vimentin expression varied across pathological T (pT) and nodal status (pN) but were not statistically significant (p = 0.964 and p = 0.334, respectively). This finding was in concordance with other studies who also did not observe significant association between vimentin expression with tumor stage and nodal status.[18,20] Khillare et al.[21] and Vora et al.[24] in their studies reported that higher vimentin expression was observed in breast carcinoma cases with lymph node metastasis and advanced stages.

In the current study, positive vimentin expression was significantly higher in TNBC subtype (57.7%) compared to Luminal (30.8%) and HER2-enriched (11.5%) subtypes. This finding is consistent with Elzamly et al.[19], Khillare et al.[21] and Yamashita et al.,[25] who reported that vimentin expression was significantly associated with triple-negative breast carcinoma, highlighting its potential role as a marker for this aggressive subtype.

Conclusion

This study demonstrated positive vimentin expression in aggressive phenotypes of infiltrating ductal carcinoma of breast, particularly in terms of higher histological

grade and TNBC subtype. This is, therefore, can be stated that vimentin may be acknowledged as an additional tool for risk assessment and prognosis prediction in IDC patients, which could aid in directing prompt treatment plans for them.

Limitations

Lymphovascular invasion was determined only by histopathological examination which may have affected the result.

Recommendations

Long term follow-up data to assess vimentin expression with disease progression, recurrence and treatment response would be beneficial to establish prognostic significance of this biomarker.

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