

Association between lymphovascular invasion (LVI) and prognostic factors in breast cancer.

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ABSTRACT:

Background: The presence of tumor cells within lymphatic or blood vessels in the surrounding tissue of a malignant tumor indicates the possibility of cancer spreading (metastasis) to other parts of the body. Lymphovascular invasion (LVI) is a significant pathogenic feature in invasive breast cancer that can provide valuable information about the tumor's aggressiveness and influence therapy options.

Objective: To the association of LVI with prognostic factors in breast cancer.

Methods: This cross-sectional study was conducted in the Department of Surgery, Sir Salimullah Medical College and Mitford Hospital, on 52 adult breast cancer patients who received Breast Conserving Surgery (BCS) or mastectomy. No patients with neoadjuvant therapy (recurring, breast cancer, metastases, or advanced breast cancer were excluded). Patients' demographic data, clinical data, and lab diagnoses were obtained. Histopathology and immunohistochemistry were performed on all samples. ER, PR, and Ki-67 were correlated with histological results. Pathologists diagnosed LVI in surgical resection tissue. All data were validated for consistency after collection. Data were analyzed using SPSS 12.0. A p value < 0.05 was considered statistically significant.

Results: The presence of ER and PR was significantly higher in cases where LVI was negative. On the other hand, the presence of Ki-67 was significantly higher in cases where LVI was positive. It was observed that cases with LVI positive had higher stages of lymph nodes metastasis and tumor grading. It was also found that the Ductal type of breast cancer was significantly higher in cases where LVI was negative. Additionally, LVI positive case was found to be significantly higher among aged people.

Conclusion: The presence of lymphovascular invasion has a negative association with ER, PR, and ductal type breast cancer and is positively associated with ki67, high grade, and greater lymph node metastasis.

Key Words:

LVI, Ki67 and breast cancer

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Introduction:

Breast cancer (BC) is the most common type of cancer in women around the world (Torre et al., 2016).¹ There are no population-based cancer records in Bangladesh. In order to treat breast cancer, it is important to find predictive and prognostic factors. The College of American Pathologists (CAP) has identified a number of prognostic and predictive factors for breast cancer that can help doctors decide how to treat breast cancer patients. Breast cancer risk factors include the number of lymph nodes present, the size of the tumor, its lymphatic and vascular invasion, the patient's age, the histologic grade, the histologic subtypes (such as tubular, mucinous, or papillary), the response to neoadjuvant therapy, and the presence of estrogen receptor (ER) or progesterone receptor (PR) or HER2 gene amplification or overexpression (Chalasanani, 2021).² Metastasis of the axillary lymph nodes is an indication that the Breast Cancer may have spread to other organs. There are five main intrinsic or molecular subtypes of Breast Cancer that are derived from immunohistochemistry (IHC) of ER/PR, HER2, and Ki 67. They are Luminal A, Luminal B, Luminal/HER2, HER2 enriched and Triple Negative (TN) subtypes. The subtypes are important to predict the biology, response to therapy and prognosis of each case. Lymphovascular invasion (LVI), which refers to the invasion of lymphatic spaces, blood vessels, or both in the peritumoral area by tumor emboli, is one of the critical steps in metastasis. The prognostic value of LVI in breast cancer was described first more than 4 decades ago (Teel, 1964).³ Subsequently, several independent studies have demonstrated a clear relation between LVI and outcome in patients with negative lymph node (LN) status^{4,7} and with some controversy, in patients with positive LN status.^{6,8,9} Routine assessment of LVI is now part of the minimum data set for breast cancer pathology reporting produced by the United Kingdom Royal College of Pathologists,¹⁰ the European Commission, and College of American Pathologists.¹¹ Moreover, LVI is associated with a poor outcome in several types of cancer such as colorectal¹², urothelial¹³, prostate¹⁴ and uterine endometrial cancer¹⁵ other than Breast Cancer. The first study on the prognostic significance of LVI in Breast Cancer was published in 1964.³ The purpose of this study was to evaluate the clinical significance of LVI in Breast Cancer.

Method:

This cross-sectional study was carried out in the Department of Surgery, Sir Salimullah Medical College and Mitford Hospital on 52 adult cases of breast cancer who underwent breast conserving surgery (BCS) or mastectomy in Department of Surgery, SSMC&MH. Patients with neoadjuvant therapy, recurrent breast carcinoma, metastasis and advanced breast carcinoma were excluded from this study.

Before taking written consent from each patients the objective of the study was discussed in details with the patients or with their attendants. Demographic along with clinical data was taken and lab diagnosis was also done. Histopathological examination and immunohistochemistry were done for all samples. For histopathological typing and grading, the tissue was stained for Hematoxylin and Eosin. The Nottingham modification of the Bloom Richardson grading system were used for histopathological grading. The immunohistochemical assay were done on de-paraffinized formalin-fixed tissue sections (thickness 3 μ m) of the samples. Then association between ER, PR and Ki-67 with the histopathological findings were evaluated. Pathologists identify LVI by examining tissue samples obtained from surgical resections under a microscope. All the collected data were recorded in a data collection form.

After collection of all the required data, these were checked, verified for consistency. Then data were inputted into the statistical software (SPSS). Collected data was analyzed by the SPSS 12.0. Categorical data were presented as frequency with percentage. Chi-square test was to see the association of LVI with ER, PR, Ki-67, lymph node staging, tumor grading and age. Spearman correlation test was performed to see the relation of Ki-67 with LVI, ER, PR and lymph node staging. For all the analysis p value < 0.05 was considered statistically significant.

Results:

Table 1: Association between LVI and other pathological factors in invasive breast cancer

	LVI		χ^2	p-value
	Positive	Negative		
ER			25.49	<0.001
Positive	0 (0.0)	25 (100.0)		
Negative	18 (66.7)	9 (33.3)		
PR			17.20	<0.001
Positive	0 (0.0)	20 (100.0)		
Negative	18 (56.3)	14 (43.8)		
Ki-67			21.75	<0.001
Positive	17 (65.4)	9 (34.6)		
Negative	01 (3.8)	25 (96.2)		
Lymph node status			39.04	<0.001
N0	0 (0.0)	14 (100.0)		
N1	0 (0.0)	16 (100.0)		
N2	11 (73.3)	4 (26.7)		
N3	7 (100.0)	0 (0.0)		
Grade of tumor			27.79	<0.001
Grade 1	0 (0.0)	20 (100.0)		
Grade 2	9 (39.1)	14 (60.9)		
Grade 3	9 (100.0)	0 (0.0)		
Type of breast carcinoma			12.81	0.002
Ductal	12 (26.1)	34 (73.9)		
Lobular	4 (100.0)	0 (0.0)		
Other	2 (100.0)	0 (0.0)		
Age			4.55	0.033
≤50	4 (18.2)	18 (81.8)		
>50	14 (46.7)	16 (53.3)		

The presence of ER and PR was significantly higher in cases where LVI was negative. On the other hand, the presence of Ki 67 was significantly higher in cases where LVI was positive. It was observed that cases with LVI positivity had higher N stages of lymph nodes and tumor grading. It was also found that the Ductal type of breast cancer was significantly higher in cases where LVI was negative. Additionally, LVI positivity was found to be significantly higher among aged people.

Discussion

In this study, maximum patients were above 50 years of age. Breast cancer was observed among the aged women.^{16,17} Some of the literature has established that breast cancer is comparatively lower among the younger population.^{18,19}

Among Ki-67 positive cases, 65.4% had LVI positive and Ki67 was positive in 50% of breast cancer patient in this study. Ki-67 expression is a predictor of breast cancer and has been identified as an independent prognostic factor in breast cancer.²⁰ High Ki-67 expression is the result of rapid tumor proliferation, which results in a poor prognosis.²¹ In the current study, patients with high Ki-67 expression had significantly high rates of LVI compared to those with low Ki-67 expression. Shen et al.²² found similar findings. In addition, a multivariate analysis showed that high Ki-67 expression is a risk factor for LVI

(OR=1.785). However, Elkablawy et al.²¹ reported that Ki-67 expression was not associated with LVI.

The frequency of tumors with definite LVI in this study was consistent with most previous studies of breast cancer (range, 25%-35% for the whole series)^{4,6,23-25}; 18%-22% for the LN-negative subgroup^{4,25} and 45%-60% for those with LN-positive tumors.^{9,24,26} The results of Rakha et al.¹⁷ demonstrate that LVI is associated with other well established prognostic variables and with patient outcomes. This prognostic value is independent of other prognostic variables, such as patient age. In this study, LVI was independent of age. In this study ER and PR were strongly positive among the LVI positive cases. Most of the high grade tumors were LVI positive (grade 3).^{27,28} According to the findings of this investigation, age did not associate significantly with ER and PR.²⁹

In breast cancer, LVI is associated with tumor size, Axillary lymph node (ALN) status, age, and histological grade, all of which are unfavorable pathological characteristics. Consistent with the negative characteristics of the four factors, it demonstrated an aggressive predictor. The method of LVI detection with hematoxylin and eosin (H&E) staining is simple and inexpensive in nearly all pathology departments; therefore, it is significant to include LVI on the list of clinical typing markers for breast cancer. Further, anti-LVI therapy could emerge as a novel therapeutic target in the context of breast cancer.³⁰

Conclusion:

Lymphovascular invasion is positively associated with ki67, high grade, higher lymph node metastasis and inversely associated with ER, PR and Ductal type of breast carcinoma.

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