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Histopathological Assessment of Tumor-Infiltrating Lymphocytes and Their Clinicopathological Associations in Breast Carcinoma- Cross Sectional Retrospective Study

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Abstract

Background: Tumor-infiltrating lymphocytes (TILs) reflect the host immune response to breast carcinoma and have emerged as important histopathological biomarkers. Increasing evidence suggests that the tumor immune microenvironment plays a crucial role in tumor behavior and its association with established clinicopathological parameters. Assessment of TILs on routine hematoxylin and eosin–stained sections provides valuable pathological information and may assist in risk stratification, particularly in resource-limited settings. However, data correlating TIL grades with clinicopathological characteristics in Indian breast cancer cohorts remain limited. ***Objective:*** To evaluate tumor-infiltrating lymphocytes in invasive breast carcinomas and to correlate their grades with clinicopathological characteristics. ***Methods:*** This retrospective study included 157 cases of histologically confirmed invasive breast carcinoma. Clinical and pathological parameters, including tumor size, histological grade, lymph node status, presence of necrosis, and histological type, were retrieved from medical records. Tumor-infiltrating lymphocytes were assessed on hematoxylin and eosin–stained sections in accordance with the recommendations of the International Tumor-Infiltrating Lymphocytes Working Group. TILs were categorized into low, intermediate, and high grades based on stromal lymphocytic density. Statistical analysis was performed using the Chi-square test to evaluate associations between TIL grades and clinicopathological variables, with a p-value <0.05 considered statistically significant. ***Results:*** Higher TIL grades showed statistically significant associations with favourable clinicopathological parameters, including smaller tumour size, lower histological grade, absence of tumor necrosis, and negative lymph node status. Certain histological subtypes, such as medullary and mucinous carcinomas, demonstrated higher TIL grades compared to invasive ductal carcinoma of no special type, indicating variation in immune response among different tumor types. ***Conclusion:*** Tumor-infiltrating lymphocyte grading demonstrates a significant association with several important clinicopathological characteristics of breast carcinoma. Routine evaluation of TILs on standard histopathological sections may serve as a simple and cost-effective adjunct parameter in pathological assessment and reporting of breast carcinoma.

Keywords: Breast Carcinoma, Clinicopathological parameters, Histological grade, Medullary carcinoma, Tumor-Infiltrating Lymphocytes.

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INTRODUCTION

Breast cancer is the most common cancer among women worldwide and is also a major cause of cancer-related deaths in India[1]. In recent years, the number of breast cancer cases has been increasing, and many patients in developing countries present at a younger age and in advanced stages of disease. Although there have been improvements in diagnosis and treatment, breast cancer shows wide variation in behavior, even among patients with similar clinical and pathological features. This highlights the need for additional markers that can help in better understanding tumor biology.

Recent studies have shown that the tumor immune microenvironment plays an important role in the development and progression of breast cancer[2]. Tumor-infiltrating lymphocytes (TILs) are immune cells present within and around the tumor tissue and represent the host immune response against cancer cells. These

lymphocytes mainly include T cells, B cells, and natural killer cells. Their presence reflects the interaction between the immune system and tumor cells, and therefore TILs have gained importance as potential prognostic and predictive markers in breast carcinoma[3].

To ensure uniform assessment, the International Tumor-Infiltrating Lymphocytes Working Group proposed standard guidelines for the evaluation of TILs on routine hematoxylin and eosin–stained sections[4]. Several studies have reported that higher levels of TILs are commonly associated with favorable clinicopathological features such as smaller tumor size, lower histological grade, and absence of lymph node metastasis. These findings have been observed more frequently in aggressive subtypes such as triple-negative and HER2-positive breast cancers5-7.

However, studies evaluating the association of TILs with clinicopathological parameters in Indian breast cancer patients are limited. Differences in genetic background, tumor characteristics, and healthcare practices may influence immune response patterns. Therefore, more data from the Indian population are required to better understand the role of TILs.

The present study aims to evaluate tumor-infiltrating lymphocytes in breast carcinomas and to correlate their grades with various clinicopathological characteristics, thereby assessing their usefulness as a simple and cost-effective parameter in routine histopathological practice.

MATERIALS AND METHODS

This retrospective study was carried out on 157 cases of histologically confirmed invasive breast carcinoma diagnosed at a tertiary care teaching hospital. Relevant clinical and pathological details were collected from hospital records and pathology registers. The parameters studied included tumor size, histological grade, lymph node status, presence or absence of necrosis, and histological type of the tumor.

Formalin-fixed, paraffin-embedded tissue blocks were retrieved, and hematoxylin and eosin–stained sections were reviewed. Tumor-infiltrating lymphocytes were evaluated on routine H&E slides according to the recommendations of the International Tumor-Infiltrating Lymphocytes Working Group. Only stromal TILs within the invasive tumor area were assessed, while areas of necrosis, fibrosis, and in situ carcinoma were excluded from evaluation.

Based on the density of lymphocytic infiltration in the tumor stroma, TILs were graded into three categories: low, intermediate, and high. Each case was assessed carefully to ensure consistency in grading. Cases with incomplete clinicopathological data were excluded from specific analyses where required.

Statistical analysis was performed using the Chi-square test to assess the association between TIL grades and various clinicopathological parameters. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Association of TIL Grade with Tumor Size (Table 1)

As shown in **Table 1**, TIL grade demonstrated a statistically significant association with tumor size ($\chi^2 = 17.33$, df = 4, p = 0.0017). Higher TIL grades were more frequently observed in tumors measuring 2–5 cm and less commonly in tumors larger than 5 cm, indicating a favorable immune response in smaller tumors.

Table 1: Association of TIL Grade with Tumour Size (n = 157)

Index	Grade 1	Grade 2	Grade 3	Total
2–5 cm	39	42	19	100
<2 cm	4	2	3	9
>5 cm	35	10	3	48
Total	78	54	25	157

Chi-square test: $\chi^2 = 17.33$, df = 4, p = 0.0017. Statistically significant association.

Association of TIL Grade with Histological Grade

Table 2 illustrates the relationship between TIL grade and histological grade. A highly significant association was observed ($\chi^2 = 48.46$, df = 4, $p < 0.001$), with higher TIL grades predominantly seen in lower histological grades, suggesting an inverse relationship between tumor aggressiveness and immune infiltration.

Table 2: Association of TIL Grade with Histological Grade (n = 157)

Index	Grade 1	Grade 2	Grade 3	Total
Grade I	0	16	0	16
Grade II	19	23	12	54
Grade III	59	15	13	87
Total	78	54	25	157

Chi-square test: $\chi^2 = 48.46$, df = 4, p = <0.001. Statistically significant association.

Association of TIL Grade with Necrosis

The association between TIL grade and necrosis is presented in **Table 3**. A statistically significant correlation was noted ($\chi^2 = 32.57$, df = 6, $p < 0.001$). Higher TIL grades were more frequently observed in tumors without necrosis, while extensive necrosis was associated with lower TIL grades.

Table 3: Association of TIL Grade with Necrosis (n = 157)

Index	Grade 1	Grade 2	Grade 3	Total
<40% present	16	20	12	48
>40% present	22	0	0	22
Absent	37	34	13	84
Present	3	0	0	3
Total	78	54	25	157

Chi-square test: $\chi^2 = 32.57$, df = 6, p = <0.001. Statistically significant association.

Association of TIL Grade with Lymph Node Status

Table 4 depicts the association between TIL grade and lymph node involvement. A significant relationship was observed ($\chi^2 = 27.26$, df = 6, $p < 0.001$). Higher TIL grades were more commonly seen in lymph node-negative cases, whereas extensive nodal involvement correlated with lower TIL grades.

Table 4: Association of TIL Grade with Lymph Node Status (n = 131)

Index	Grade 1	Grade 2	Grade 3	Total
1–3 positive	22	14	6	42
4–9 positive	12	11	0	23
>9 positive	18	0	0	18
Negative	16	25	7	48
Total	68	50	13	131

Chi-square test: $\chi^2 = 27.26$, df = 6, p = <0.001. Statistically significant association.

Association of TIL Grade with Histological Type

As shown in **Table 5**, TIL grade varied significantly across different histological types ($\chi^2 = 100.77$, df = 20, $p < 0.001$). Medullary and mucinous carcinomas demonstrated higher TIL grades compared to invasive ductal carcinoma, indicating a stronger immune response in these subtypes.

Table 5: Association of TIL Grade with Histological Type (n = 157)

Index	Grade 1	Grade 2	Grade 3	Total
IDC	72	33	15	120
IDC with NE	1	2	0	3
IDC with medullary features	0	0	7	7
IDC with medullary patterns	0	0	3	3
IDC with mucinous	0	5	0	5
IDC with squamous	4	0	0	4
Mixed Invasive Ductal Carcinoma (50% IDC and Papillary carcins)	1	0	0	1
Mixed Mucinous breast carcinoma with NE (up to 50% mucinous)	0	3	0	3
lobular carcinoma	0	2	0	2
mixed invasive and lobular carcinoma	0	2	0	2
mucinous carcinoma	0	7	0	7
Total	78	54	25	157

Chi-square test: $\chi^2 = 100.77$, df = 20, p = <0.001. Statistically significant association.

Overall analysis showed that tumor-infiltrating lymphocyte (TIL) grades had a statistically significant association with all the studied clinicopathological parameters. TIL grade was significantly related to tumor size, histological grade, presence of necrosis, lymph node status, and histological type. Higher TIL grades were more commonly observed in smaller tumors, lower histological grades, tumors without necrosis, and lymph node–negative cases. Certain histological subtypes also

demonstrated higher TIL levels. These findings indicate that increased lymphocytic infiltration is associated with more favorable clinicopathological features in breast carcinoma.

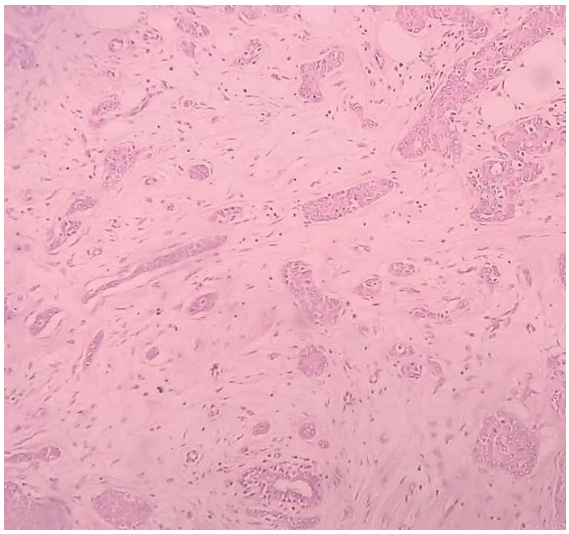

Figure 1: TIL grade: Low

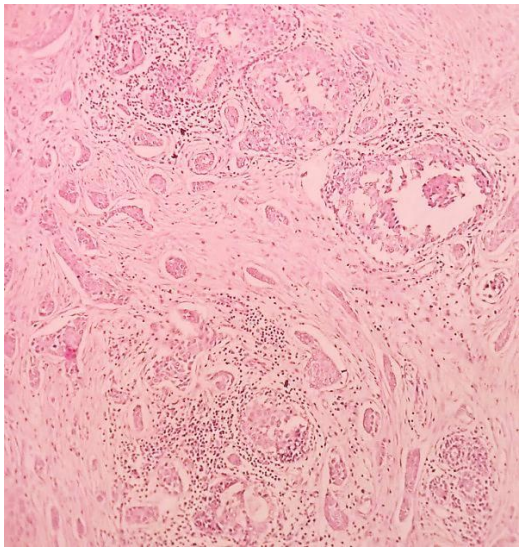

Figure 2: TIL grade: Intermediate

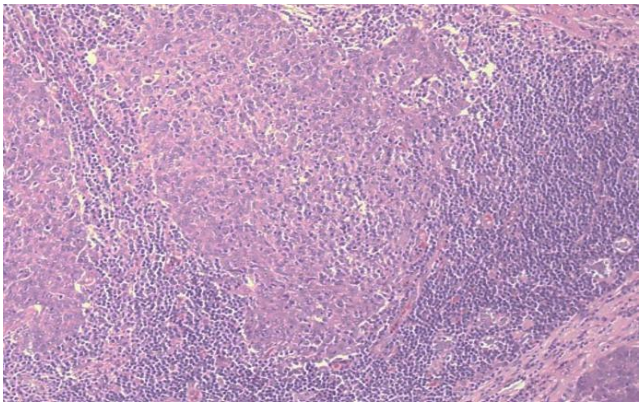

Figure 3: TIL grade: Hight

DISCUSSION

Tumor-infiltrating lymphocytes represent the host immune response against tumor cells and have gained increasing importance in breast carcinoma. In the present study, TIL grades showed a significant association with

several clinicopathological parameters, indicating their potential role in reflecting tumor behavior.

In this study, higher TIL grades were more commonly seen in smaller tumors. Similar observations have been reported by Salgado et al. and Denkert et al., who found that tumors with higher immune infiltration were often associated with favorable tumor characteristics[4,5]. This suggests that an active immune response may limit tumor growth.

A significant association was also observed between TIL grade and histological grade, with higher TIL grades seen in lower-grade tumors. This finding is in agreement with studies by Loi et al. and Vaid et al., who reported an inverse relationship between tumor grade and lymphocytic infiltration[6,7]. Lower-grade tumors may provide a more favorable environment for immune cell infiltration compared to poorly differentiated tumors.

Lymph node status also showed a significant correlation with TIL grade. Higher TIL grades were more frequently observed in lymph node–negative cases. This observation is consistent with studies by Tsang et al. and Thanna et al., who reported lower rates of nodal metastasis in tumors with higher immune cell infiltration 8,9,[10].

The present study demonstrated that tumors without necrosis showed higher TIL grades. Similar findings were reported by Marchetti et al., who suggested that extensive necrosis may be associated with aggressive tumor behavior and reduced immune response[11].

Regarding histological type, medullary and mucinous carcinomas demonstrated higher TIL grades compared to invasive ductal carcinoma of no special type. This finding supports previous observations that certain histological subtypes are more immunogenic in nature.

Overall, the findings of this study support the usefulness of TIL grading as a simple histopathological parameter that correlates well with established clinicopathological features in breast carcinoma.

CONCLUSION

Tumor-infiltrating lymphocytes show a significant association with key clinicopathological characteristics of breast carcinoma. Higher TIL grades correlate with favorable prognostic parameters, suggesting their potential role as a simple, cost-effective prognostic biomarker in routine pathology practice.

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