Original Article

Prevalence of Stromal Tumor Infiltrating Lymphocytes in Invasive Breast Carcinoma

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Abstract

Background: Tumor-infiltrating lymphocytes (TILs) represent the host immune response within the breast cancer microenvironment and are increasingly recognized as histopathological biomarkers with potential prognostic and predictive significance. However, their distribution across molecular subtypes and disease stages in routine diagnostic practice remains incompletely characterized, particularly in pathology-based cohorts. Aim: To assess the prevalence of stromal TILs in invasive breast carcinoma and evaluate their association with molecular subtypes and pathological stage.
Methods: This prospective study included 70 patients with invasive breast carcinoma. Molecular subtyping was performed using immunohistochemistry for estrogen receptor, progesterone receptor, HER2, and Ki-67, with fluorescence in situ hybridization for HER2-equivocal cases. Stromal TILs were evaluated on hematoxylin and eosin–stained sections according to International TILs Working Group recommendations and recorded as the percentage of stromal area occupied by mononuclear inflammatory cells. TILs were categorized as low (0–10%), intermediate (11–59%), or high (≥60%). Associations between TIL levels, molecular subtype, and stage were analyzed using chi-square or Fisher's exact tests.
Results: The overall mean stromal TIL score was 31.3% (median 10%). Luminal HER2-negative low Ki-67 tumors demonstrated the lowest infiltration (mean 19.3%; 81% low TILs). Luminal HER2-negative high Ki-67 tumors showed relatively higher immune activity (mean 40.4%; 54% intermediate/high). HER2-positive tumors exhibited predominantly low-to-intermediate infiltration, while triple-negative breast cancers showed the greatest heterogeneity. Among early-stage cases, 63% had low TILs, whereas advanced-stage tumors showed only low-to-intermediate levels. No statistically significant associations were observed.
Conclusion: Stromal TIL distribution varies by molecular subtype, with greater immune activity in proliferative luminal, HER2-positive, and triple-negative tumors. Routine histopathological assessment of TILs offers a simple, reproducible, and cost-effective approach for evaluating tumor–immune interaction and may support prognostication and therapeutic stratification.

Keywords: tumor-infiltrating lymphocytes (TIL); breast cancer; molecular subtypes; TNBC; HER2; Ki-67; prognosis

Introduction

The assessment of tumor-infiltrating lymphocytes (TILs) in breast cancer (BC) has gained importance over the past decade. TILs are present in all molecular subtypes; however, their prevalence varies, with higher immune infiltration observed in

triple-negative breast cancer (TNBC) and HER2-positive tumors compared with luminal-type cancers [1, 2]. Several studies report a decline in TIL density with disease progression, suggesting immune evasion from early to advanced stages [3].

The clinical validity, prognostic and predictive significance of TILs have been widely investigated. Most studies focus on stromal TILs, as defined by the International TILs Working Group [4], due to their reproducibility and ease of assessment on routine histopathology sections. High stromal TIL levels are strong prognostic markers in early-stage TNBC, both in patients receiving adjuvant therapy and those managed without adjuvant treatment [5, 6, 7]. Similarly, in early HER2-positive breast cancer treated with adjuvant therapy, increased TIL levels are associated with improved outcomes and may help identify patient subsets suitable for treatment de-escalation [3].

In contrast, TILs have not demonstrated consistent prognostic value in luminal-type breast cancer, where immune infiltration is generally lower and its clinical significance remains uncertain [8]. However, tumors with high proliferative activity, indicated by elevated Ki-67 expression, show a positive association between high TIL levels and favourable prognosis, while tumors with low Ki-67 demonstrate an inverse relationship [9]. In the neoadjuvant setting, higher TIL density in pretreatment biopsies predicts pathological complete response across breast cancer subtypes [10, 11]. In TNBC, evaluation of TILs in residual disease following neoadjuvant chemotherapy provides additional prognostic information with therapeutic implications [12, 13].

In the era of immunotherapy, although PD-L1 assays are utilized, their interpretation is limited by variability in testing methodologies and clinical contexts, including differences in assay platforms, scoring systems, cut-offs, and tumor-immune scoring algorithms [14]. Consequently, histopathological assessment of stromal TILs has been proposed as a surrogate marker for PD-L1 to aid in selecting patients for immunotherapy, as stromal TIL levels correlate with PD-L1 expression and reflect immune activation that may predict response to immune checkpoint blockade [15, 16]. This study provides real-world, pathology-based data on stromal TIL distribution using standardized assessment in a routine diagnostic setting, reflecting practical applicability in resource-limited environments where advanced molecular assays may not be universally available.

Aim & Objectives

The aim of this study was to assess the prevalence of stromal tumor-infiltrating lymphocytes in invasive breast carcinoma. The objectives were to classify invasive breast carcinoma into molecular subtypes using immunohistochemistry and fluorescence in situ hybridization, to assess average TIL scores in the overall cohort and in individual subtypes, and to evaluate the association of TILs with molecular subtypes in early- and advanced-stage disease in a pathology-based cohort.

Material and Methods

This prospective study was conducted in the Department of Pathology, Sri Venkateswara Institute of Medical Sciences, Tirupati, from October 2021 to September 2023. Formalin-fixed (10% buffered formalin) resection specimens of invasive breast carcinoma were processed using standard histopathological techniques. Four-micrometer sections were stained with hematoxylin and eosin and evaluated according to College of American Pathologists guidelines.

Only cases with histopathological confirmation of invasive breast carcinoma and complete clinicopathological and staging data were included. Patients who had received neoadjuvant therapy, core biopsy specimens, and tumors with incomplete molecular subtype information were excluded.

Immunohistochemistry (IHC) was performed for estrogen receptor (ER; clone SP1, Ventana), progesterone receptor (PR; clone 1E2, Ventana), HER2/neu (polyclonal, Dako), and Ki-67 (clone MIB-1, Biogenex). HER2-equivocal (2+) cases were further evaluated using fluorescence in situ hybridization. Ki-67 labelling index was recorded as the percentage of positively stained tumor nuclei in areas of highest proliferative activity, and tumors were classified as low ($<$20%) or high ($\geq$20%) proliferation based on established thresholds for luminal breast cancer stratification [17].

Molecular subtyping was performed using ER, PR, HER2, and Ki-67 status. Stromal tumor-infiltrating lymphocytes (TILs) were assessed on hematoxylin and eosin–stained sections according to International TILs Working Group recommendations and expressed as the percentage of stromal area occupied by mononuclear inflammatory cells. TILs were analyzed as continuous variables and categorized as low (0–10%), intermediate (11–59%), or high ($\geq$60%).

Statistical analysis was performed using the chi-square test to evaluate associations between categorical variables. The assumptions of the chi-square test were assessed by examining expected cell frequencies. When expected counts in any cell were less than five, particularly in sparsely populated categories such as advanced-stage tumors, Fisher's exact test was applied as a more appropriate alternative. A p-value $<$0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 25 (Armonk, NY: IBM Corp).

Results

A total of 70 cases of invasive breast carcinoma were included in the study. Histologically, invasive ductal carcinoma of no special type constituted majority of cases (n=67), with one case each of mucinous, cribriform, and metaplastic carcinoma. Tumor grading revealed 17 (24%) grade I, 33 (47%) grade II, and 20 (29%) grade III tumors. Lymph vascular invasion was identified in 35 cases. Tumor size distribution showed 14 T1, 48 T2, and 8 T3 tumors. Nodal assessment demonstrated no metastasis in 38 cases, while the remaining cases showed varying degrees of nodal involvement N1 to N3 (13 N1a, 2 N1mi, 11 N2a, and 6 N3a).

Based on pathological staging, 60 cases were categorized as early-stage disease and 10 as advanced-stage disease. Molecular classification using immunohistochemistry and fluorescence in situ hybridization identified four subtypes: luminal HER2-negative low Ki-67, luminal HER2-negative high Ki-67, HER2-positive, and triple-negative breast cancer (TNBC). Ki-67 labeling index was categorized as low ($<$20%) and high ($\geq$20%) for subgroup stratification. These are summarized and shown in Table 1.

Table 1: Classification into subtypes and average TIL score (continuous value) in each subtype.

Subtype	Number (n)	Average TIL score	Median TIL score
Luminal, HER2−, Low Ki-67	21	19.33	10
Luminal, HER2−, High Ki-67	11	40.45	59
HER2+	25	33.52	10
TNBC	13	32	10
Total	70	31.325	10

The overall mean stromal tumor-infiltrating lymphocyte (TIL) score for the cohort was 31.3%, with a median value of 10%. Luminal HER2-negative tumors with low Ki-67 ($<$20%) consistently demonstrated lower stromal TIL infiltration, with majority of cases falling within the low TIL category (0–10%) shown in Figure 1. In contrast, luminal HER2-negative tumors with high Ki-67 ($\geq$20%) exhibited relatively higher immune activity, with an increased proportion of intermediate (11–59%) and occasional high ($\geq$60%) TIL scores. HER2-positive tumors showed a mixed distribution, predominantly within the low-to-intermediate categories. TNBC demonstrated marked heterogeneity, with cases distributed across low, intermediate, and high TIL groups.

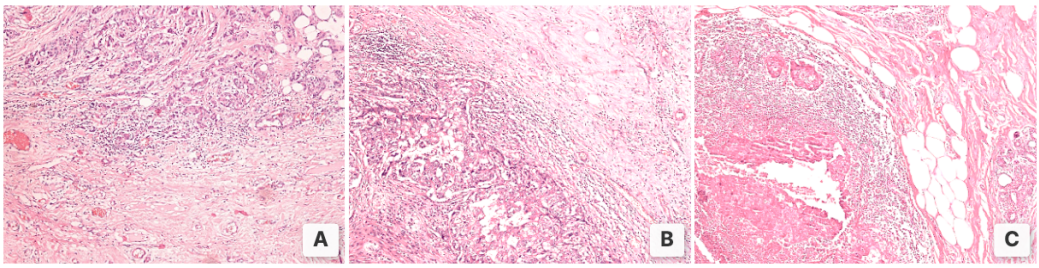

Figure 1: A. Microphotograph showing invasive breast carcinoma with low TILs (0–10%) [Hematoxylin & Eosin, x200]. B. Microphotograph showing invasive breast carcinoma with intermediate TILs (11–59%) [Hematoxylin & Eosin, x200]. C. Microphotograph showing invasive breast carcinoma with high TILs ($\geq$60%) [Hematoxylin & Eosin, x200].

Subtype-wise analysis of categorical TIL distribution (Table 2) showed that 81% of luminal HER2-negative low Ki-67 tumors had low TILs, whereas luminal HER2-negative high Ki-67 tumors demonstrated nearly equal distribution between low and intermediate categories, with a small proportion of high TILs. HER2-positive tumors were almost equally distributed between low and intermediate infiltration. Among TNBC cases, most demonstrated low-to-intermediate TILs, with a minority showing high infiltration.

Table 2: Association of TIL score (categorical value) with each subtype of breast carcinoma.

Subtype	Total n (%)	TILs low (0–10%)	TILs intermediate (11–59%)	TILs high (≥60%)	P value
Luminal, HER2−, Low Ki-67	21 (30%)	17 (81%)	4 (19%)	0	0.17
Luminal, HER2−, High Ki-67	11 (16%)	5 (45%)	5 (45%)	1 (9%)	
HER2+	25 (36%)	13 (52%)	12 (48%)	0	
TNBC	13 (18%)	8 (62%)	4 (31%)	1 (8%)	

Stage-wise analysis demonstrated that among early-stage tumors (n=60) (Table 3), 38 (63%) showed low TILs, 20 (33%) intermediate, and 2 (4%) high infiltration. In advanced-stage tumors (n=10) shown in Table 4, only low and intermediate

TIL categories were observed. High TIL levels were not recorded in this subgroup. However, due to the limited number of advanced-stage cases, this observation should be interpreted descriptively.

Table 3: Association of TIL score (categorical value) with early-stage breast carcinoma of each subtype.

Subtype	Number of patients n (%)	TILs low (0–10%) n (%)	TILs intermediate (11–59%) n (%)	TILs high (≥60%) n (%)	P value
Luminal, HER2−, Low Ki-67	19 (32%)	15 (79%)	4 (21%)	0	0.237
Luminal, HER2−, High Ki-67	9 (32%)	5 (56%)	3 (33%)	1 (11%)	
HER2+	20 (34%)	10 (50%)	10 (50%)	0	
TNBC	12 (20%)	8 (67%)	3 (25%)	1 (8%)	
Total	60 (100%)	38 (63%)	20 (33%)	2 (4%)	

Table 4: Association of TIL score (categorical value) with advanced stage of each subtype.

Subtype	Number of patients n (%)	TILs low (0–10%) n (%)	TILs intermediate (11–59%) n (%)	TILs high (≥60%) n (%)	P value
Luminal, HER2−, Low Ki-67	2 (20%)	2 (100%)	0	0	0.158
Luminal, HER2−, High Ki-67	2 (20%)	0	2 (100%)	0	
HER2+	5 (50%)	3 (60%)	2 (40%)	0	
TNBC	1 (10%)	0	1 (100%)	0	
Total	10 (100%)	5 (50%)	5 (50%)	0	

Comparative statistical analysis between molecular subtype, stage, and TIL categories was performed using chi-square or Fisher's exact tests where appropriate. None of the observed associations reached statistical significance (all p values >0.05).

Overall, stromal TIL assessment across the cohort demonstrated subtype-specific variability, with lower immune infiltration in luminal low-proliferative tumors and greater heterogeneity in HER2-positive and triple-negative breast cancers (Table 5).

Table 5: Association of TIL score (categorical value) with molecular subtypes and stage.

Molecular subtype	Number of patients n	Stage	Number of patients n (%)	TILs low (0–10%)	TILs intermediate (11–59%)	TILs high (≥60%)	P value
Luminal, HER2−, Low Ki-67 BC	21	Early Advanced	19 (90%) 2 (10%)	15 (79%) 2 (100%)	4 (21%) 0	0 0	1.0
Luminal, HER2−, High Ki-67 BC	11	Early Advanced	9 (82%) 2 (18%)	3 (33.33%) 2 (100%)	1 (11.11%) 0	5 (55.55%) 0	0.231
HER2+ BC	25	Early Advanced	20 (80%) 5 (20%)	10 (50%) 2 (40%)	0 0	10 (50%) 3 (60%)	1
TNBC	13	Early Advanced	12 (92%) 1 (8%)	3 (25%) 1 (100%)	1 (8%) 0	8 (67%) 0	0.296

Discussion

Tumor-infiltrating lymphocytes (TILs) represent the host immune response against malignant cells and have emerged as important components of the breast cancer microenvironment. Increasing evidence supports their value as histopathological biomarkers with both prognostic and predictive implications, particularly in triple-negative and HER2-positive breast cancers. In the present study, we evaluated the prevalence and distribution of stromal TILs across molecular subtypes and disease stages in a routine diagnostic cohort using standardized criteria. Although statistically significant associations were not identified, distinct subtype-specific immune patterns were observed, reflecting biologically meaningful trends that are concordant with established literature.

Luminal HER2-negative tumors with low Ki-67 expression consistently demonstrated minimal stromal TIL infiltration in our series, highlighting an immunologically quiescent or "cold" tumor microenvironment. Similar findings have been reported in hormone receptor–positive, low-proliferative breast cancers, where reduced genomic instability and lower neoantigen load may result in limited immune activation and diminished lymphocytic recruitment [18, 8]. These tumors are often characterized by slower growth kinetics and weaker inflammatory signaling, which may explain the relatively sparse immune

infiltrate observed histologically. The predominance of low TIL levels in this subgroup further supports the concept that immune engagement is closely linked to tumor biology rather than merely histological subtype.

In contrast, luminal HER2-negative tumors with higher proliferative indices demonstrated relatively increased TIL infiltration. This observation aligns with reports suggesting that tumor proliferation and mitotic activity are associated with enhanced antigenicity and increased interaction with the host immune system [3, 18, 19]. Elevated Ki-67 expression reflects rapid cell turnover and may contribute to greater neoantigen exposure, thereby stimulating lymphocytic recruitment. These findings reinforce the notion that proliferative status, rather than hormone receptor expression alone, may be a more relevant determinant of immune infiltration within luminal tumors, underscoring the biological heterogeneity within this group.

HER2-positive tumors in our study demonstrated predominantly low-to-intermediate TIL levels with moderate heterogeneity. Several investigations have documented immune activation in HER2-amplified breast cancers, where tumor-associated antigens and antibody-mediated mechanisms promote lymphocytic response [20, 21]. Stromal TIL density in HER2-positive disease has been shown to correlate with improved response to trastuzumab-based therapy and favorable outcomes, suggesting that immune engagement enhances therapeutic efficacy. The distribution of TILs observed in our cohort is directionally consistent with these reports and supports the biological plausibility of immune-mediated effects in this subtype.

Triple-negative breast cancer demonstrated the widest variability in stromal TIL levels, reflecting its well-recognized biological diversity. TNBC is frequently regarded as the most immunogenic molecular subtype, and numerous studies have shown that higher TIL density correlates with improved pathological complete response to chemotherapy and superior survival outcomes [22, 23]. The heterogeneity noted in our cases is likely due to intrinsic molecular differences within TNBC, where some tumors exhibit marked immune activation while others remain relatively immune desert–like. This variability highlights the importance of direct histopathological assessment rather than assuming uniform immunogenicity.

When stratified by disease stage, most tumors exhibited low-to-intermediate TIL infiltration. High TIL levels were not observed among the small number of advanced-stage tumors, and no statistically significant association between TIL category and stage was identified. These observations suggest that immune infiltration may be driven more strongly by intrinsic tumor biology than by anatomical extent of disease. Immune–tumor interactions remain complex and dynamic, influenced by both tumor-intrinsic and microenvironmental factors.

From a practical perspective, histopathological evaluation of stromal TILs offers several advantages. Assessment can be performed on routine hematoxylin and eosin–stained sections without additional reagents or specialized equipment, making it inexpensive and widely accessible. The standardized methodology recommended by the International TILs Working Group provides reproducible criteria that can be readily incorporated into routine reporting [4], which might serve as a feasible surrogate indicator of tumor–host immune interaction.

Beyond prognostic implications, TIL assessment may assist therapeutic decision-making. Increasing evidence indicates that tumors with greater immune infiltration are more likely to respond to systemic therapies, including chemotherapy, targeted therapy, and emerging immunotherapeutic approaches [2, 24]. Tumors with higher stromal TIL levels may represent immunologically “hot” phenotypes and could potentially benefit from immune checkpoint inhibitors, thereby supporting the utility of routine TIL assessment in identifying candidates for immunotherapy, particularly in triple-negative and HER2-positive disease. Identification of immunologically active tumors through simple histological methods may therefore facilitate patient stratification and guide personalized management strategies especially in settings where PD-L1 testing or advanced molecular assays are not readily available. Consequently, routine documentation of TIL levels may enhance the translational relevance of standard pathology practice.

Overall, the present study provides real-world insight into stromal TIL distribution across breast cancer subtypes within a tertiary-care diagnostic setting. The observed immune patterns are consistent with established biological principles and contemporary literature, reinforcing the role of stromal TILs as meaningful indicators of tumor–immune interaction and supporting their integration into routine histopathological reporting.

Limitations of the study

Clinical outcome measures such as overall or disease-free survival were not evaluated, as this study was designed as a pathology-based descriptive analysis using resection specimens and uniform longitudinal follow-up was not available. The prognostic relevance of stromal TILs in triple-negative and HER2-positive breast cancers has already been well established in large prospective studies. Therefore, the present work focuses primarily on the distribution and histopathological assessment of TILs in routine diagnostic practice. Future studies incorporating systematic follow-up are warranted to validate survival correlations in this population. Despite limitations related to sample size, our study adds to the growing body of evidence supporting TILs as indicators of tumor–host immune interaction and as cost-effective prognostic markers, particularly relevant in resource-limited settings.

Conclusion

This study demonstrates that stromal tumor-infiltrating lymphocyte (TIL) distribution in invasive breast carcinoma varies according to molecular subtype and reflects underlying tumor biology. Luminal HER2-negative tumors with low proliferative activity consistently exhibited minimal immune infiltration, suggesting an immunologically "cold" microenvironment, whereas luminal tumors with higher Ki-67 indices, HER2-positive cancers, and triple-negative breast cancers showed relatively greater immune heterogeneity and intermediate-to-high stromal TIL levels. Triple-negative tumors displayed the widest variability, underscoring their biological diversity and differing immune phenotypes.

Although high TIL levels were not observed in the small subset of advanced-stage tumors, this finding should be interpreted descriptively due to limited sample size, and definitive conclusions regarding stage-related differences cannot be drawn. No statistically significant associations were identified, likely reflecting cohort size rather than absence of biological trends.

Overall, the observed subtype-specific immune patterns are consistent with established evidence that immune infiltration is closely linked to tumor proliferation and molecular characteristics rather than anatomical stage alone. Routine histopathological evaluation of stromal TILs on hematoxylin and eosin sections offers a simple, reproducible, and cost-effective method for assessing tumor–host immune interaction. Incorporation of standardized TIL assessment into routine reporting may provide clinically meaningful information for prognostication and therapeutic stratification. Larger, multicentric studies with outcome correlation are warranted to further establish the clinical utility of stromal TILs in breast cancer management.

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