JK SCIENCE pISSN: 0972-1177

ORIGINAL ARTICLE

Assessment of Tumor Infiltrating Lymphocytes in Breast Cancer Patients and its Correlation with Clinico-Histopathological Characteristics and Molecular Subtypes

Nanda J Patil, Suresh Bhosle*, Sujata R. Kanetkar, Neha Ghadge

Abstract

Background: Scoring of tumor infiltrating lymphocytes (TIL's) in breast carcinomaspecimens has gained increasing value as it has prognostic and predictive value in certain molecular subtypes of breast cancer especially triple negative breast cancer. The present study evaluated tumor infiltrating lymphocyte in breast carcinoma cases and correlated the response with age of the patient, tumor size, tumor grade, histopathological subtypes and molecular classification. **Material and Methods:** A cross-sectional observational study was conducted on 104 cases of invasive breast carcinoma from January 2024 to march 2025. Clinicopathological details like age of the patient, tumor size, histopathological type of tumor with grade and molecular classification were taken into account. Assessment of TIL was done based on International TIL working group recommendations and correlations were evaluated. **Results:** A total of 104 cases were studied. Majority of patients belonged to age group of 41 years to 50 year. Higher TIL response was found in young patients (<40years). 53.8%were having tumor size of 3cm to 5 cm. Cases with tumor size <3 cm have revealed highest TILresponse. Maximum number of patients (66%) were having grade 3 tumor with marked TIL response (55%). Invasive duct carcinoma was the frequent diagnosis. Higher TIL was found in metaplastic carcinoma cases (75%). Majority of cases (39.4%) were luminal A subtype. Triple negative cases (basal type) showed highest TIL score (68.7%). **Conclusion:** This study validates the histomorphological evaluation of tumor-infiltrating lymphocytes as proposed by the International TILs Working Group in the Indian population and highlights its role as a cost-effective prognostic immune biomarker.

Key Words

Breast Cancer, Clinical Features, Tumor Infiltrating Lymphocytes, Molecular Classification

Introduction

Breast cancer is a biologically heterogeneous disease characterized by diverse histological patterns, molecular alterations, clinical behavior, and response to therapy. It is one of the leading causes of cancer-related mortality among women worldwide[1]. According to the WHO 2022 classification, breast carcinomas are conventionally categorized based on histomorphology; however, most tumors fall under invasive ductal carcinoma or invasive lobular carcinoma, limiting adequate representation of biological heterogeneity.

Department of Pathology, *Department of Surgery, Krishna VishwaVidyapeeth, Karad, Maharashtra, India.
Correspondence to: Ghadge Neha, Tutor, Department of Pathology, Krishna Vishwa Vidyapeeth, Karad, Maharashtra, India.
Manuscript Received: 11.11.2025; **Revision Accepted**: 10.02.2026
Published Online First: 10th April, 2026
Open Access at: https://journal.jkscience.org

Cite this article as: Patil NJ, Bhosle S, Kanetkar SR, Ghadge N. Assessment of Tumor Infiltrating Lymphocytes in Breast Cancer Patients and its Correlation with Clinico-Histopathological Characteristics and Molecular Subtypes. JK Science 2026; 28(2):87-91.

Molecular classification of breast cancer has improved prognostic stratification and therapeutic decision-making. The interaction between tumor cells and the host immune system plays a crucial role in tumor progression. Tumor-infiltrating lymphocytes (TILs) represent a surrogate marker of adaptive immune response and have been associated with improved outcomes in several breast cancer subtypes, particularly in triple-negative and HER2-positive tumors[2,3]. Assessment of TILs on routine hematoxylin and eosin-stained sections is simple, reproducible, and cost-effective. This is especially relevant in low-resource settings like India, where access to advanced molecular techniques may be limited. Incorporation of TIL assessment can aid prognostication and guide therapeutic strategies, particularly in aggressive breast cancer subtypes.

Primary objective is to assess tumor infiltrating lymphocytes in invasive breast carcinoma and secondary objective is to correlate TIL response with age of the patient, tumor size, histological grade, histopathological subtype, and molecular classification.

Materials and Methods

This was a cross-sectional study carried out in the Histopathology Department at our tertiary care centre, from January 2024 to March 2025. A total of 104 breast carcinoma cases were included over a period of 14 months based on consecutive universal sampling (time bound study where all Histopathologically confirmed invasive breast carcinoma cases fulfilling inclusion and exclusion criteria were included). Cases were selected based on inclusion and exclusion criteria:

- **Inclusion criteria:** Histopathologically confirmed breast carcinoma cases received as wide local excision or modified radical mastectomy specimens.
- **Exclusion criteria:** In situ carcinomas, post-neoadjuvant cases and cases with recurrence.

Ethical consideration – Ethical approval for this study was done by Institutional Ethical Committee (IEC no- KVV/IEC/04/2025; Date – 13/05/2025).

For histological assessment, tissue samples were fixed in 10% neutral buffered formalin and processed by standard paraffin embedding. Sections were cut at 4 µm and stained with H&E stain.

Grading and Subtyping

Histologic Grading: Assessed per the Nottingham grading system (tubule formation, nuclear pleomorphism, and mitotic rate)[1].

Tumor Subtyping: Based on WHO 5th Edition classification using morphological criteria.

Molecular classification: Micro sections were subjected to immunohistochemistry (IHC) using antibodies to estrogen receptor(ER), progesterone receptor (PgR), HER2/Neu. The scoring of ER, PR, HER2/Neu staining in the positive cases was done as per American Society of Clinical Oncology and the College of American pathologist (ASCO/CAP) guidelines using Allred scoring system. The Allred score is the sum of proportion (proportion of stained nuclei of cells) and the intensity score (intensity of stained nuclei). Positive interpretation requires at least 1% of tumor cells showing positive nuclear staining of any intensity. ASCO/CAP guidelines were followed for Her2neu reporting and 3+ staining (uniform intense membrane staining of >10% tumor cells) was considered as positive, 0 and 1+ staining as negative and 2+ as equivocal[4].

TLR Evaluation: Tumor-infiltrating lymphocytes were evaluated according to the International TILs Working Group guidelines[5]. Stromal TILs within the invasive tumor area were assessed and categorized as no response, mild (<10%), moderate (11–40%), or marked (>40%)[6].

Tumor infiltrating response was evaluated inside the invasive tumor nests.

Data Analysis was done based on descriptive statistics summarized patient demographics, tumor grades, molecular classification and TIL response scores. Chi-square and ANOVA were used to analyze associations between TIL response, histologic grade, and tumor subtype. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS v26.

Results

Total 104 cases were studied within a period of January 2024 to March 2025.

Discussion

Prognostic value of TIL assessment in breast cancer has been studied by various authors[7]. St Gallen has concerned about application of TIL evaluation and its inclusion in the clinical practice for better clinical impact[5]. We have analyzed different patterns of TIL in various histological subtypes of breast cancer as well as its correlation with age of the patient, tumor size, tumor grade, tumor subtype and molecular classification. In relation to age, our study has found marked TIL score in younger age group (30 – 40 years). Least TIL score was seen in the age group >70 years. Similar observation has

Table 1 : Distribution of Casesaccording to Age of Patient, Tumor Size, Tumor Subtype, Tumor Grade and Molecular Classification.

Age Distribution	Number of Cases (N = 104)	Percentages of Cases
30 – 40 years	20 cases	19.2%
41 – 50 years	38 cases	36.5%
51 – 60 years	22 cases	21.1%
61 – 70 years	09 cases	8.6%
>70 years	15 cases	14.4%
Tumor size (in cm)		
Less than 3 cm	28 cases	26.9%
3cm to 5cm	56 cases	53.8%
More than 5 cm	20cases	19.2%
Tumor subtype		
Invasive Duct Carcinoma	75 cases	72.1%
Mixed type of carcinoma	15 cases	14.4%
Invasive Lobular Carcinoma	8 cases	7.6%
Metaplastic Breast Carcinoma	4 cases	3.8%
Mucinous Carcinoma	2 cases	1.9%
Tumor grade		
Grade 1	6 cases	5.7%
Grade 2	29 cases	27.8%
Grade 3	69 cases	66.3%
Molecular classification of tumor		
Luminal A	41cases	39.4%
Luminal B	14 cases	13.4%
Her2 enriched	17 cases	16.3%
Basal type	32 cases	30.7%

been noted by Camille verocq et al[8,9,10]. We have compared TILscorewith tumor size. Marked TIL response was observed in patients with tumor size <3 cm,while no response was seen in patient with tumor size >5 cm. Similar observation has been noted by Marchatti et al[11,12].We have classified these breast cancer cases based on recent WHO classification, 72% patients belonged to Invasive ductal carcinoma no special type and remaining were mixed type carcinoma (14.4%), Invasive lobular carcinoma (7.6%), Metaplastic carcinoma (3.8%) and Mucinous carcinoma (1.9%). Marked TIL score was seen in metaplastic breast carcinoma (75%) followed by invasive duct carcinoma (42.6%) while no TIL response was found in 50% of mucinous carcinoma and 46% of mixed type carcinoma. We have compared TIL in different grades of breast carcinoma cases. In this study most of the grade 1 tumors (66.6%) showed no TIL response while 55%of grade 3 tumors revealed marked TIL which is statistically significant. Similar observation has been noted by different studies[13,14]. We classified cases based on molecular classification. Majority of cases belonged to luminal type (53%) followed by basal type (30.7%) and then Her2 enriched (16.3%) which is statistically significant. Similar observation has been noted by different studies[15,16,17,18]. Highest TIL response was observed in basal type breast carcinoma cases (68.7%) while lowest response was seen in luminal subtypes (36%). Amongst luminal subtypes maximum (43.9%) luminal A casesshowed no TIL response while marked TIL score was seen in only 7.3% luminal A cases. Similar results have been noted by Mohitkumar et al[11], Pooja M Vaid et al[19].

From this study it was observed that TIL score has highly significant statistical correlation with tumor grade and molecular classification of breast cancer cases.Higher response was seen with young age, small tumor size, higher tumor grade, and metaplastic carcinoma cases. Basal type breast cancer cases showed marked response thus TIL score serves as potential prognostic marker to

Table 2 : Correlation of TIL Response with Age of Patient, Tumor Size, Tumor Subtype, Tumor Grade and Molecular Classification.

Age distribution	No TILs	Mild TILs	Moderate TILs	Marked TILs	Total cases (N = 104)	P value
30 – 40 years	06 (30%)	04 (20%)	00 (00)	10 (50%)	20	0.33 (NS)
41 – 50 years	10 (26.3%)	05 (13.1%)	06 (15.7%)	17 (44.7%)	38	
51 – 60 years	04 (18.1%)	05 (22.7%)	06 (27.2%)	07 (31.8%)	22	
61 – 70 years	02 (22.2%)	03 (33.3%)	00 (00)	04 (44.4%)	09	
>70 years	08 (53.3%)	04 (26.6%)	01 (6.6%)	02 (13.3%)	15	
Tumor size (in cm)						
Less than 3 cm	06 (4.4%)	05 (17.8%)	02 (7.1%)	15 (53.5%)	28	0.35 (NS)
3cm to 5cm	16 (28.5%)	13 (23.2%)	07 (12.5%)	20 (35.7%)	56	
More than 5 cm	08 (40%)	03 (15%)	04 (20%)	05 (25%)	20	
Tumor subtype						
Invasive Duct Carcinoma	20 (26.6%)	13 (17.3%)	10 (13.3%)	32 (42.6%)	75	0.05 (significant)
Mixed type of carcinoma	07 (46.6%)	03 (20%)	02 (13.3%)	03 (20%)	15	
Invasive Lobular Carcinoma	03 (37.5%)	03 (37.5%)	00 (00%)	02 (25%)	8	
Metaplastic Breast Carcinoma	00 (00%)	00 (00%)	01 (25%)	03 (75%)	4	
Mucinous Carcinoma	01 (50%)	00 (00%)	01 (50%)	00 (00%)	2	
Tumor grade						
Grade 1	04 (66.6%)	00	01 (16.6%)	01 (16.6%)	06	<0.001 (Highly significant)
Grade 2	17 (58.6%)	10 (34.4%)	01 (3.4%)	01 (3.4%)	29	
Grade 3	10 (14.4%)	10 (14.4%)	11 (15.9%)	38 (55%)	69	
Molecular classification						
Luminal A	18 (43.9%)	13 (31.7%)	07 (17.0%)	3 (7.3%)	41	<0.001 (Highly significant)
Luminal B	02 (14.2%)	05 (35.7%)	03 (21.4%)	4 (28.5%)	14	
Her2 enriched	05 (29.4%)	03 (17.6%)	01 (5.8%)	8 (47%)	17	
Basal type	05 (15.6%)	03 (9.2%)	02 (6.2%)	22 (68.7%)	32	

Abbreviations: TILs – Tumor-Infiltrating Lymphocytes; IDC – Invasive Duct Carcinoma; ILC – Invasive Lobular Carcinoma; NS – Not Significant. **Statistical test:** Chi-square test. * Significant at $p< 0.05$; Highly significant at $p< 0.001$.

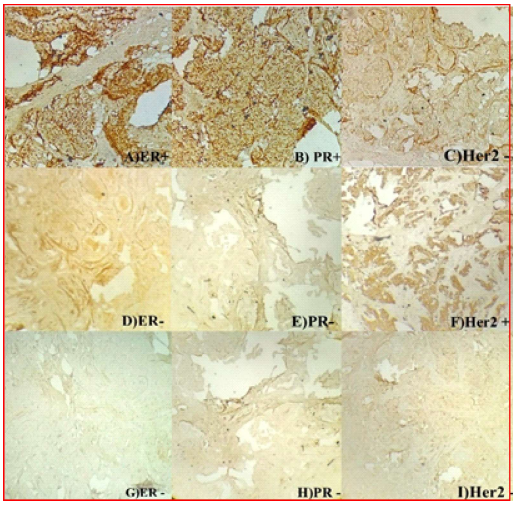

Figure 1: Molecular Subtypes - A, B, C) Luminal A (100X); D, E, F) Her2 Enriched 100X; G, H, I) Basal Like (Triple negative; 100X)

expensive chemotherapy. Also it is cost effective diagnostic tool in low resources countries like India.

Conclusion

Tumor-infiltrating lymphocyte scoring serves as a valuable and cost-effective prognostic tool in breast cancer, particularly in basal-like subtypes. Its assessment using routine histopathological techniques makes it suitable for implementation in low-resource settings and telepathology services.

Financial Support and Sponsorship : Nil
Conflict of Interest: Nil

References

1. Mittal A, Mani NS. Molecular classification of breast cancer. Indian J Pathol Oncol. 2021;8(2):241–7.
2. Loi S, Michiels S, Salgado R, Sirtaine N, Jose V, Fumagalli D, et al. Tumor infiltrating lymphocytes are prognostic in triple-negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER

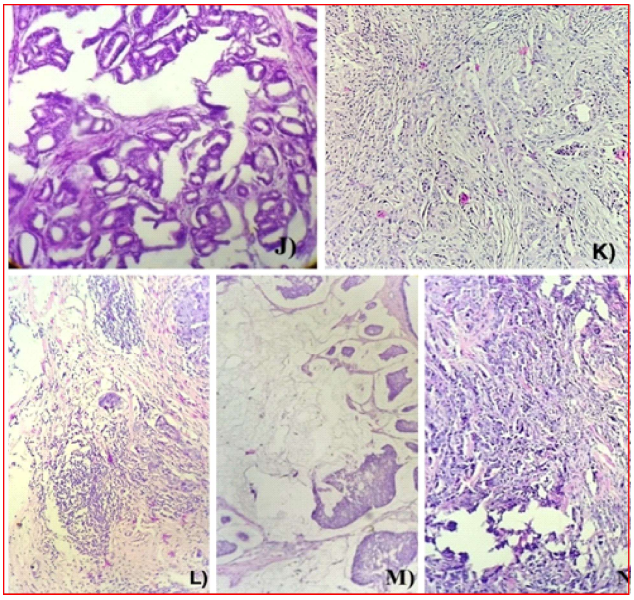

Figure 2: J; Invasive Breast Carcinoma No Special Type Grade 1, no TIL Response (100X H & E); K: Invasive Breast Carcinoma No Special Type Grade 2, TIL Response 1(100X H &E); L: Invasive Breast Carcinoma No Special Type Grade 3 TIL Response 3(100X H &E); M: Mucinous Carcinoma, TIL Response 0 (100X H &E); N: Pleomorphic Lobular Carcinoma, TIL Response 0 (100X H &E)

trial. Ann Oncol. 2014;25(8):1544–50.
3. Adams S, Gray RJ, Demaria S, Goldstein L, Perez EA, Shulman LN, et al. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. J Clin Oncol. 2014;32(27):2959–66.
4. Devadass CW, Royal AB, Saxena P, Devraj D, Gouri M. Breast carcinoma: correlation of molecular subtypes with histopathologic characteristics. J Med Sci Health. 2023;9(3):281–7.
5. Salgado R, Denkert C, Demaria S, Sirtaine N, Klauschen F, Pruneri G, et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Ann Oncol. 2015;26(2):259–271.
6. Rangan R, Kanetkar SR, Bhosale SJ, Mane DA, Patil NJ, Gudur RA. Assessment of intratumoural and stromal infiltrating lymphocytes in various subtypes of breast carcinoma patients who received neoadjuvant chemotherapy. Asian Pac J Cancer Prev. 2023;24(7):2347–52.
7. Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the primary therapy of early breast cancer 2015. Ann Oncol. 2015;26(8):1533–46.
8. Verocq C, Noël JC, Charry M, Zindy E, Rorive S, Salmon I, et al. Inverse correlation between the amounts of lymphocytic infiltrate and stroma in breast carcinoma. Heliyon. 2024;10(22):e40295.
9. El Bairi K, Haynes HR, Blackley E, Fineberg S, Shear J, Turner S, et al. The tale of TILs in breast cancer: a report from the International Immuno-Oncology Biomarker Working Group. NPJ Breast Cancer. 2021;7:150.
10. Takada K, Kashiwagi S, Asano Y, Goto W, Morisaki T, Shibutani M, et al. Differences in tumor-infiltrating lymphocyte density and prognostic factors for breast cancer by patient age. World J Surg Oncol. 2022;20(1):38.
11. Kumar M, Eshwaraiah C, Bedtur KPA, Rudrappa S, Mariappa. Correlation of tumor-infiltrating lymphocytes with tumor staging and grading in breast carcinomas: a retrospective study. Int J Sci Res Dent Med Sci. 2023;5(1):16–20.
12. Macchetti AH, Marana HR, Silva JS, Andrade JM, Ribeiro-Silva A, Bighetti S. Tumor-infiltrating CD4+ T lymphocytes in early breast cancer reflect lymph node involvement. Clinics (Sao Paulo). 2006;61(3):203–08.
13. Criscitiello C, Vingiani A, Maisonneuve P, Viale G, Curigliano G. Tumor-infiltrating lymphocytes (TILs) in ER+/HER2- breast cancer. Breast Cancer Res Treat. 2020;183(2):347–54.
14. de Jong VM, Wang Y, Ter Hoeve ND, Opdam M, Stathonikos N, JóŸwiak K, et al. Prognostic value of stromal tumor-infiltrating lymphocytes in young, node-negative, triple-negative breast cancer patients who did not receive (neo)adjuvant systemic therapy. J Clin Oncol. 2022;40(21):2361–74.
15. Onitilo AA, Engel JM, Greenlee RT, Mukesh BN. Breast cancer subtypes based on ER/PR and HER2 expression: comparison of clinicopathologic features and survival. Clin Med Res. 2009;7(1–2):4–13.
16. Setyawati Y, Rahmawati Y, Widodo I, Ghozali A, Purnomosari D. The association between molecular subtypes of breast cancer with histological grade and lymph node metastases in Indonesian women. Asian Pac J Cancer Prev. 2018;19(5):1263–8.
17. Geethamala K, Murthy S, Vani BR, Rao S. Histopathological grade versus hormone receptor status in breast carcinoma. Int J Biomed Res. 2015;6(7):466–471.
18. Walke V, Gunjkar G. Immunohistochemical profile and its association with clinicopathological parameters in carcinoma breast: a prospective study in central India. Int J Res Med Sci. 2019;7(5):1796–801.
19. Vaid PM, Puntambekar AK, Jumle NS, Banale RA, Ansari D, Reddy RR, et al. Evaluation of tumor-infiltrating lymphocytes in molecular subtypes of an Indian cohort of breast cancer patients. Diagn Pathol. 2022;17(1):91.