# Prognostic value of tumor infiltrating lymphocyte in metastatic breast cancer

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## Abstract:

**Background:** Breast cancer (BC) is a heterogeneous disease with multiple subtypes. Despite various new treatment strategies, several trials were conducted to improve outcomes, particularly in metastatic BC, due to low survival rates. Previously, BC was not thought to be immunologically active, especially when compared to melanoma. However, a recent study has revealed that the presence of tumor-infiltrating lymphocytes (TILs) in between and surrounding tumor cells may be beneficial, and the increased density of TILs was associated with a better prognosis. We conducted this study to evaluate the prognostic impact of TILs in metastatic BC patients.

**Material and Method:** One hundred and five patients with metastatic breast cancer were prospectively recruited at the Medical Oncology Department, South Egypt Cancer Institute, in the period from January 2018 to January 2020. The median follow-up duration was 17 months The relationship between TILs and clinicopathological features and survival outcomes in metastatic BC patients was evaluated.

**Result:** High TILs and ER-negative (p=0.000), Her2/neu overexpression (p=0.000), and triple-negative BC (TNBC) (p=0.031 were found to have statistically significant differences. High TILs had a positive prognostic effect on PFS and OS in patients with TNBC. High TILs were significantly associated with improved PFS in patients with HER2/neu overexpression tumors but had no effect on OS.

**Conclusion:** There is a strong correlation between hormonal and Her2/neu status of BC and TILs density. High TILs density has favorable outcomes regarding OS and PFS, particularly in TNBC in metastatic cases.

**Trial registration:** South Egypt Cancer Institute ethics committee, SECI-IRB, number IORG0006563-468

**Keyword:** Tumor infiltrating lymphocytes; metastatic breast cancer; overall survival; Triple negative breast cancer

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## Introduction:

Breast cancer (BC) is the first common cancer in women in the USA. The lifetime risk of developing BC is 13%, and one in eight women has the possibility of developing BC [1]. With the transition from local stage 0 or 1A cancer to metastatic stage IV cancer, the five-year survival rates for BC patients drop from 99 percent to just 27 percent, increasing the necessity for a systemic treatment that can eliminate both microscopic and macroscopic metastases [2]. BC accounts for 18.9% of all malignancies in Egypt, with 5-year survival rates of around 97 % and 20% for early and metastatic stages, respectively [3].

In most malignancies, the immunological microenvironment is a delicate balance between immune cells mediating tissue damage and immune cells striving to prevent it. The significant way the immune system can identify and eradicate cancer is adaptive immunity, which is defined as an immune response that needs antigen-specific detection of the tumor. There has been evidence of a link between tumor growth and immune cells [4]. Tumor-infiltrating lymphocytes (TILs), particularly antitumor type 1 lymphocyte infiltration, have been linked to a better prognosis in a variety of tumor types, including colon [5], ovarian [6], lung [7], and breast cancer [8].

BC has not been considered immunologically active in the past, especially compared to cancers like melanoma [9]. Recent research suggests, however, that the presence of TILs in BC prior to treatment can

predict treatment response and enhance prognosis [10]. The cytotoxic action of TILs against tumors was the initial focus. [11] Surveillance is carried out by the system, and it is possible to eliminate it. Immunosurveillance is a method of monitoring nascent malignancies. Infiltrating inflammatory cells, particularly lymphocytes and macrophages, frequently surround tumor cells. There is strong evidence that cells of the adaptive immune system have been found in murine studies [12,13].

TILs consist of three types of cells: T cells, B cells, and natural killer (NK) cells, which comprise roughly 75%, 20%, and 5% of TILs in BC, respectively [14]. Cytotoxic (CD8+) T cells are possible biomarkers of the tumor-associated immune response since they are a prominent component of the adaptive immune system [15].

Most prior investigations of CD8+ T cells in BC have found a link to a better prognosis [15]. The majority of TILs in invasive duct carcinoma patients were found at tumor margins or superficial regions, with a few found in the tumor bed, especially in patients with high-grade malignancies [11]. TILs are related to high-proliferative, high-grade, and estrogen receptor (ER)-negative tumors at baseline, and they are a significant predictive factor for specific BC subtypes, particularly triple-negative breast cancer (TNBC)[16]. A study gives evidence of the cytotoxic T-cell population's predictive significance in BC despite immunoediting, implying that cytotoxic T cells have a clinically considerable antitumoral effect against human BC [17]. Chemotherapy, hormonal therapy, targeted therapy, and immunotherapy are among the systemic treatment choices for patients with metastatic BC. Patients with higher numbers of total TILs have better treatment success with each of these regimens [18–21].

Several studies have documented that stromal TILs were preferable and more easily applicable than intratumoral TILs, which can be attributed to the intratumoral TILs present in the lower count, heterogeneous, and their evaluation on H&E-stained slides being difficult without immunohistochemistry aid. In addition, intratumoral TILs scores were aligned with stromal TILs. Consequently, no additional data will get from its scoring [22].

This study was conducted to evaluate the prognostic role of TILs density and its relation to clinicopathological features in stage IV breast cancer.

## Material and Methods:

*Study design and patients methods*

Between January 2018 and January 2020, a prospective observational study was conducted at the Medical Oncology Department, South Egypt Cancer Institute, Assiut University, on 105 newly diagnosed metastatic breast cancer patients. Pathologically confirmed BC, age ≥ 18 years with a performance status of ≤2, and adequate hematological, hepatic, and renal functions were the inclusion criteria. Patients with no documentation, pregnant or breastfeeding, and those with synchronous cancer or cancer within the preceding five years were also excluded. Our institutional ethics committee, SECI-IRB, granted us ethical permission under the number IORG0006563-468 and written consent has been obtained from patients under the study.

*Assessment and treatment of the breast cancer cases*

All BC patients were subjected to a thorough baseline examination, including a review of their medical history, physical examination, pathological data, clinical examination, and radiological diagnostic (CT/MRI +/- bone scan). Chemotherapy with various agents was one type of systemic treatment dependent on the physician's choice AC (Adriamycin and cyclophosphamide), FAC (fluorouracil, Adriamycin, and cyclophosphamide), FEC (fluorouracil, Epirubicin, and cyclophosphamide), Taxanes, Gemcitabine plus carboplatin, vinorelbine plus capecitabine or liposomal doxorubicin along with targeted therapy (Trastuzumab or lapatinib) in patients with HER2/neu positive. Hormonal therapy, including tamoxifen or aromatase inhibitors, was administered to women with positive hormonal receptors BC. Re-evaluation of treatment response according to Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 used [23]. Overall survival (OS) was calculated from the time of the start of therapy to the date of death due to any cause. Progression-free survival (PFS) was calculated from the time of the start of treatment till the date of disease progression or death. The percentage of patients with the best overall response obtained throughout the trial with complete response (CR), complete response indeterminate (Cri), or partial response (PR) as judged by the investigator were referred to as the best overall response rate (BOR).

*Evaluation of TILs*

Examination of H&E stained slides of BC tissue sections using Olympus microscope CX22 at ×200 magnification. Evaluation of stromal TILs, which represent the percentage of mononuclear immune cells (lymphocytes and plasma cells), existed in the stroma between the tumor cells, provided that they do not adhere to tumor nests. In the current study, two scoring systems for TILS were used. The first one has divided the BC patients into Lymphocyte-predominant BC (LPBC) and Lymphocyte-trivial BC (LTBC) subtypes with a cut-off of 50%. The second evaluation system was the tree tire system that stratified BC patients into mild TILS (0-10%), Intermediated TILs (>10-<40%), and dense TILs (≥40%) [22] (figure 1).

*Statistical methods:*

All statistical calculations were done using SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) version 22. Data were statistically described in terms of frequencies (number of cases) and relative frequencies (percentages). Chi-square ($\chi 2$) test was performed to compare categorical data. Kaplan-Meier's method with log-rank test was used to calculate overall and progression-free survival analysis. P-value

is always two-tailed, with the level of significance set at 0.05.

## Results:

*Demographic Data and clinicopathologic features*

One hundred-five patients have been studied for TILs density, 75 were LTBC, and 30 were LPBC. While using the three-tire system, 50 patients had mild stromal TILs, 50 had moderate TILs, and five had dense TILs. The detailed patients demographic and clinicopathologic parameters are described in Table 1.

*Association between TILs and clinicopathological features*

Table.1 depicts the association between TILs density and clinicopathologic variables, using both a cut-off value of 50% and a three-tire method for patient stratification according to TILs density. TILs dense aggregates were significantly associated with histological grade 3 (p=0.035). No significant association was present between the patient's age, menstrual status, tumor size, lymph node status, or lymphovascular invasion (LVI).

Regarding hormonal receptor status, LPBC significantly associated with negative ER (p=0.000), negative PR (p=0.000), and regarding to breast cancer molecular subtypes; LPBC are associated with Non luminal A subtypes (P=0.001), non-luminal B (p= 0.015), HER2 overexpression (p=0.000) and TNBC subtypes (p=0.031) (Table 2) (figure 1). Comparison between lymphocytic infiltration and different intrinsic subtypes is done where the luminal A and B associated with LTBC while TNBC and HER2 enriched are sociated with LPBC.

As regard distant metastasis, mild TILs was significantly associated with no visceral crises (p=0.017). No significant association was found between TILs and the site or number of metastasis (Table 3).

*Response to treatment and TILs density*

No statistically significant association was found between the density of TILs and the response rate to different treatment lines (Table 4).

*Survival outcomes and TILs density*

In patients with TNBC subtype, LPBC had a significantly higher PFS (p= 0.003) and OS (p=0.000) in comparison with LTBC. While in patients with HER 2/neu overexpression tumors, the LPBC was significantly associated with higher PFS (p=0.002), without a significant impact of on OS (p=0.331). figure 2

**Table 1** Association between TILs density and patient's characteristics

| Variable name | Total patients NO. (%) | 2 tire TILs | | | 3 tire TILs | | | |
|---|---|---|---|---|---|---|---|---|
| | | **LTBC NO. (%)** | **LPBC NO. (%)** | **P** | **Mild TILs NO (%)** | **Moderate TILs NO (%)** | **Dense TILs NO (%)** | **P** |
| Age groups (years) | | | | 0.577 | | | | 0.341 |
| • < 50 | 57 (54.3) | 42 (56.0) | 15 (50.0) | | 28 (56.0) | 28 (56.0) | 1 (20.0) | |
| • ≥ 50 | 48 (45.7) | 33 (44.0) | 15 (50.0) | | 22 (44.0) | 22 (44.0) | 4 (80.0) | |
| Menstruation status | | | | 0.288 | | | | 0.220 |
| • Premenopausal | 61 (58.1) | 46 (61.3) | 15 (50.0) | | 29 (58.0) | 31(62.0) | 1 (20.0) | |
| • Postmenopausal | 44 (41.9) | 29 (38.7) | 15 (50.0) | | 21 (42.0) | 19 (38.0) | 4 (80.0) | |
| Tumor size | | | | 0.802 | | | | 0.757 |
| • T1+T2 | 61 (58.1) | 43 (57.3) | 18 (60.0) | | 29 (58.0) | 30(60.0) | 2 (40.0) | |
| • T3+T4 | 44 (41.9) | 32 (42.7) | 12 (40.0) | | 21 (42.0) | 20 (40.0) | 3 (60.0) | |
| LN status | | | | 0.298 | | | | 0.565 |
| • N0+N1 | 36 (34.3) | 28 (37.3) | 8 (26.7) | | 20 (40.0) | 15 (30.0) | 1 (20.0) | |
| • N2+N3 | 69 (65.7) | 47 (62.7) | 22 (73.3) | | 30 (60.0) | 35 (70.0) | 4 (80.0) | |
| Tumor grade | | | | 0.378 | | | | **0.035*** |
| • Grade II | 86 (81.9) | 63 (84.0) | 23 (76.7) | | 44 (88.0) | 40 (80.0) | 2 (40.0) | |
| • Grade III | 19 (18.1) | 12 (16.0) | 7 (23.3) | | 6 (12.0) | 10 (20.0) | 3 (60.0) | |
| DCIS | | | | 0.322 | | | | 0.431 |
| • Absent | 57 (54.3) | 43 (57.3) | 14 (46.7) | | 25 (50.0) | 28 (56.0) | 4 (80.0) | |
| • Present | 48 (45.7) | 32 (42.7) | 16 (53.3) | | 25 (50.0) | 22 (44.0) | 1 (20.0) | |
| LVI | | | | 0.569 | | | | 0.382 |
| • No | 64 (61.0) | 47 (62.7) | 17 (56.7) | | 34 (68.0) | 27 (54.0) | 3 (60.0) | |
| • Yes | 41 (39.0) | 28 (37.3) | 13 (43.3) | | 16 (32.0) | 23 (46.0) | 2 (40.0) | |
| Peri-neural invasion | | | | 0.702 | | | | 0.657 |
| • No | 66 (62.9) | 48 (64.0) | 18 (60.0) | | 34 (68.0) | 29 (58.0) | 3 (60.0) | |
| • Yes | 39 (37.1) | 27 (36.0) | 12 (40.0) | | 16 (32.0) | 21 (42.0) | 2 (40.0) | |

*, Significant; N, Number; TILs, Tumor infiltrating lymphocytes; LN, Lymph node; LVI, Lymphovascular invasion; LPBC, Lymphocyte predominant breast cancer; LTBC, Lymphocyte trivial breast cancer.

**Table 2** Association between TILs density and the hormonal status of the studied participants

| Hormonal status | 2-tire TILs | | | 3- tire TIL | | | |
|---|---|---|---|---|---|---|---|
| | **LTBC N (%)** | **LPBC N (%)** | **P** | **Mild TILS N (%)** | **Moderate TILS N (%)** | **Dense TILS N (%)** | **P** |
| ER | | | **0.000*** | | | | **0.001*** |
| • Negative | 12 (16.0) | 21(70.0) | | 10 (20.0) | 18(36.0) | 5(100.0) | |
| • Positive | 63 (84.0) | 9 (30.0) | | 40 (80.0) | 32 (64.0) | 0 (0.0) | |
| PR | | | **0.000*** | | | | **0.017*** |
| • Negative | 20 (26.7) | 23 (76.7) | | 17 (34.0) | 21 (42.0) | 5(100.0) | |
| • Positive | 55 (73.3) | 7 (23.3) | | 33 (66.0) | 29 (58.0) | 0 (0.0) | |
| HER2 | | | 0.730 | | | | 0.809 |
| • Negative | 55 (73.3) | 21 (70.0) | | 36 (72.0) | 37 (74.0) | 3 (60.0) | |
| • Positive | 20 (26.7) | 9 (30.0) | | 14 (28.0) | 13 (26.0) | 2 (40.0) | |
| Luminal A | | | **0.001*** | | | | **0.049*** |
| • No | 34 (45.3) | 27 (90.0) | | 23 (46.0) | 30 (60.0) | 5 (100.0) | |
| • Yes | 41 (54.7) | 3 (10.0) | | 27 (54.0) | 20 (40.0) | 0 (0.0) | |
| Luminal B | | | **0.015*** | | | | 0.352 |
| • No | 49 (65.3) | 23 (76.7) | | 34 (68.0) | 37 (74.0) | 5 (100.0) | |
| • Yes | 26 (34.7) | 7 (23.3) | | 16 (32.0) | 13 (26.0) | 0 (0.0) | |
| Her2 overexpression | | | **0.000*** | | | | 0.055 |
| • No | 72 (96.0) | 16 (53.3) | | 46 (92.0) | 39 (78.0) | 3 (60.0) | |
| • Yes | 3 (4.0) | 14 (46.7) | | 4 (8.0) | 11 (22.0) | 2 (40.0) | |
| TNBC | | | **0.031*** | | | | **0.017*** |
| • No | 69 (92.0) | 23 (76.7) | | 46(92.0) | 44 (88.0) | 2 (40.0) | |
| • Yes | 6 (8.0) | 7 (23.3) | | 4 (48.0) | 6 (12.0) | 3(60.0) | |
| Intrinsic subtypes of BC | | | **0.000*** | | | | **0.006*** |
| • Luminal A | 40 (53.3) | 6 (20.0) | | 26 (52.0) | 20 (40.0) | 0 (0.0) | |
| • Luminal B | 26 (34.7) | 3 (10.0) | | 16 (32.0) | 13 (26.0) | 0 (0.0) | |
| • Her2 overexpression | 3 (4.0) | 14 (46.7) | | 4 (8.0) | 11 (22.0) | 2 (40.0) | |
| • TNBC | 6 (8.0) | 7 (23.3) | | 4 (8.0) | 6 (12.0) | 3 (60.0) | |

*, Significant; N, Number; TILs, Tumor infiltrating lymphocytes; LPBC, Lymphocyte predominant breast cancer; LTBC, Lymphocyte trivial breast cancer; TNBC, Triple negative breast cancer.

**Table 3** Association between TILs and tumor metastasis among the studied participants

| **Distant metastasis** | **2-tire TIL** | | | **3-tire TIL** | | | |
|---|---|---|---|---|---|---|---|
| | **LTBC N (%)** | **LPBC N (%)** | **P** | **Mild stromal TILS N (%)** | **Moderate stromal TILS N (%)** | **Dense stromal TILS N (%)** | **P value** |
| **Visceral** | | | 0.259 | | | | 0.217 |
| • No | 17(22.7) | 10(33.3) | | 11(22.0) | 13(26.0) | 3(60.0) | |
| • Yes | 58(77.3) | 20(66.7) | | 39(78.0) | 37(74.0) | 2(40.0) | |
| **Non visceral metastasis** | | | 0.259 | | | | 0.217 |
| • No | 58(77.3) | 20(66.7) | | 39(78.0) | 37(74.0) | 2(40.0) | |
| • Yes | 17(22.7) | 10(33.3) | | 11(22.0) | 13(26.0) | 3(60.0) | |
| **Number of metastases** | | | 0.516 | | | | 0.672 |
| • Single | 38(50.7) | 18(60.0) | | 25(50.0) | 29(58.0) | 2(40.0) | |
| • Multiple | 37(49.3) | 12(40.0) | | 25(50.0) | 21(42.0) | 3(60.0) | |
| **Visceral crisis** | | | 0.623 | | | | **0.017*** |
| • No | 63(84.0) | 24(80.0) | | 46(92.0) | 36(72.0) | 5(100.0) | |
| • Yes | 12(16.0) | 6(20.0) | | 4(8.0) | 14(28.0) | 0(0.0) | |

*, Significant; N, Number; TILs, Tumor infiltrating lymphocytes; LPBC, Lymphocyte predominant breast cancer; LTBC, Lymphocyte trivial breast cancer

**Table 4** Association between TILs and the radiological response of the studied participants

| Radiological response | 2-tire TIL | | | 3-tire TIL | | | |
|---|---|---|---|---|---|---|---|
| | **LTBC N (%)** | **LPBC N (%)** | **P** | **Mild TILS N (%)** | **Moderate TILS N (%)** | **Dense TILS N (%)** | **P** |
| **First line** | | | 0.921 | | | | 0.567 |
| • Overall response | 41(54.7) | 15(53.6) | | 26(52.0) | 26(54.2) | 4(80.0) | |
| • PD | 34(45.3) | 13(46.4) | | 24(48.0) | 22(45.8) | 1(20.0) | |
| **Second line** | | | 0.483 | | | | 0.072 |
| • Overall response | 37(64.9) | 13(56.5) | | 29(74.4) | 18(50.0) | 3(60.0) | |
| • PD | 20(35.1) | 10(43.5) | | 10(25.6) | 18(50.0) | 2(40.0) | |
| **Third line** | | | 0.057 | | | | 1 |
| • Overall response | 14(60.9) | 2(20.0) | | 7(50.0) | 8(47.1) | 1(50.0) | |
| • PD | 9(39.1) | 8(80.0) | | 7(50.0) | 9(52.9) | 1(50.0) | |
| **Best response for the three lines** | | | 0.456 | | | | 0.172 |
| • Overall response | 41(54.7) | 13(46.4) | | 30(60.0) | 23(47.9) | 1(20.0) | |
| • PD | 34(45.3) | 15(53.6) | | 20(40.0) | 25(52.1) | 4(80.0) | |

N, Number; TILs, Tumor infiltrating lymphocytes; LPBC, Lymphocyte predominant breast cancer; LTBC, Lymphocyte trivial breast cancer;

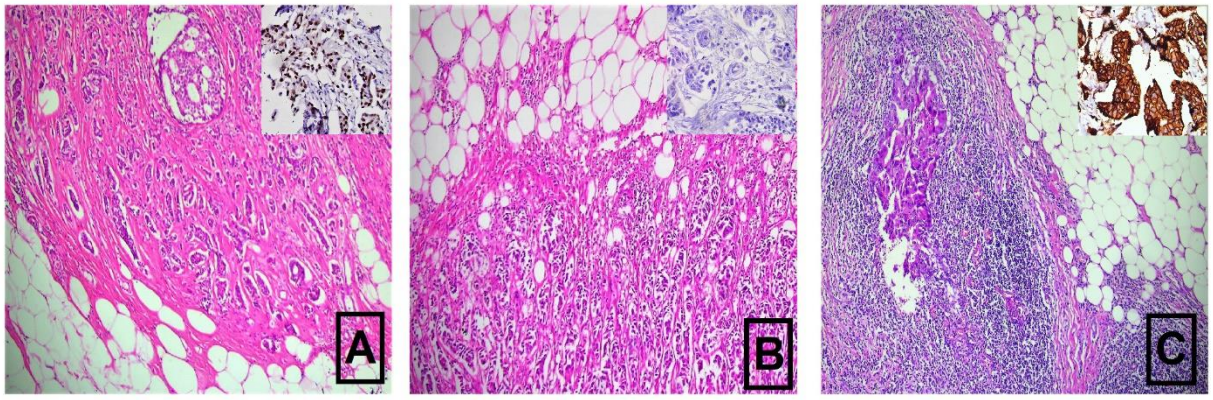


**Fig. 1 Stromal TILs density in invasive duct carcinoma of breast.** (a) Mild stromal TILs density (X 20), inset showed ER positive staining in the same case (X 40). (b) Moderate stromal TILs density (X 20), inset showed triple negative staining in the same case (X 40) (c) High stromal TILs density (X 20), inset showed Her2/neu positive staining in the same case (X 40).

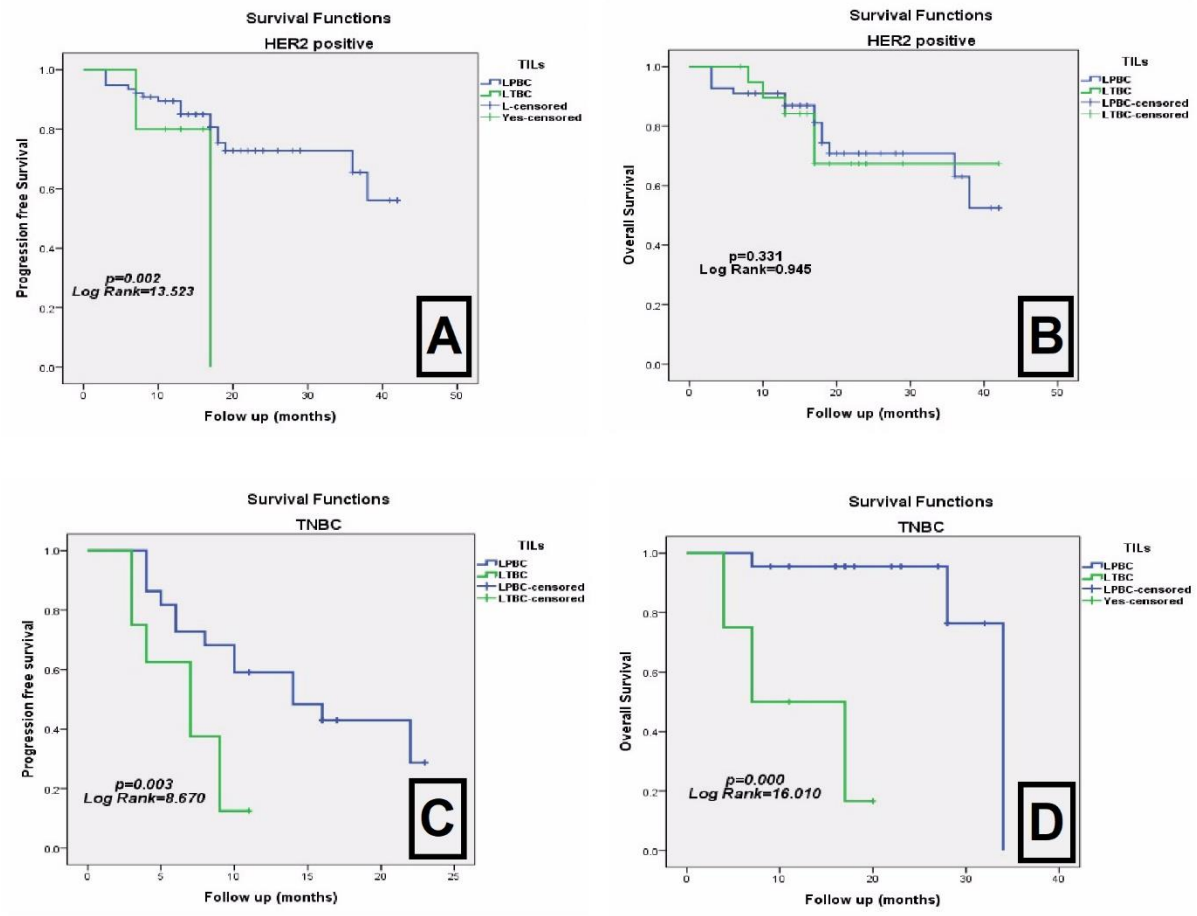


**Fig. 2 Survival outcomes and TILs density.** (a) In patients with TNBC subtype, LPBC had a good prognostic effect on PFS and (b) prolonged OS. (c) In patients with HER 2 /neu overexpression tumors, the LPBC were significantly associated with higher PFS. (d) No significant impact of TILs on OS.

## Discussion:

The fact that tumor cells escape the immune system has an impact on the prognosis of BC patients has been a hot topic in the past few years. There were several studies on this issue.[24] TNBC is an aggressive molecular subtype of BC with the least choices for systemic therapy comparable with luminal and HER2-positive invasive BC subtypes. Furthermore, there are no proven markers for TNBC prognosis [25]. Recently, plenty of research has been focused on studying the value of the immune system as a prognostic parameter and response determinant in invasive BC, especially TNBC [26].

In the current study, TIL density was found to have a statistically significant association with high histological grade. This finding aligns with previous studies done by Ishigami et al. (2019) [11], Mahmoud SMA et al. (2011) [17], and Denkert (2010) [22]. A positive relationship was present between histologic tumor grade and hormonal and Her2/neu status [27]. With the higher grade, the more frequency of hormonal negative tumor, Her2/neu positive, or TNBC.[28] The current work described a significant association between stromal-rich TILs and hormonal negative tumor with or without Her2/neu overexpression, as well as TNBC. These findings are consistent with that of Mahmoud et al. (2011) [17], Chung et al. (2017) [29], Lui et al. 2014 [30], and Pujani et al. 2020 [31]. Research conducted by Ishigami et al. (2019) was incompatible with the current finding as they found no significant difference between TILs density and hormonal receptors (HR) positive and HER2 positive. This conflict resulted from using B regulatory and T regulatory cells [11].

On the other hand, we found no statistically significant difference between high and low TILs density and patients age, tumor size, lymph node status and LVI this was also matched by studies conducted previously [11],[18],[29].

It is generally known that antitumor immune responses are focused in the draining lymph nodes and tumor site. Our observations, however, suggest that this could also occur in patient with visceral crisis.

The present study revealed that no difference found between treatment lines variation in TILS density. This discordant with Asano et al (2020) study that evaluated relationship between TILS density and response to endocrine therapy in metastatic setting,

which found that a high level of stromal TILs had a role in the therapeutic efficacy of endocrine therapy for patients with ER positive stage IV BC [17]. This discrepancy may be due different sample size and inclusion of all BC subtype with multimodality of therapy in our study. Another study found an increase in the response rate and higher TILS in neoadjuvvant setting particularly with anthracyclin based chemotherapy [32].

Regarding OS and PFS, the present study documented that TNBC patients with LPBC associated with increase OS and PFS this finding concordant with several trials [16]. This result are different from that reported by Bates et al. (2006) study that found no association between survival outcome and high TILS associated hormonal receptors. This contradiction attributed to the outcome analysis done focused on T regulatory cells subpopulation [33]. Furthermore, Her2/neu overexpression BC patients with LPBC showed also high PFS. This matched with Stanton e al (2016) study [26]. However, this result in contrast with a study conducted by Mahmoud et al (2011), where they found that the OS better with HER2 negative rather than positive BC. This discrepancy may be explained by different sample size [17]. Moreover, a study conducted by Loi et al (2013) found no association between HER2 overexpression and TILs in survival outcomes. [34] Another study showed better outcome in cases with high TILS associated luminal A and HER2 positive subtypes. This study disclosed that increase the number of examined core biopsy associated with more significant results suggesting TILS heterogeneity among various tumor area [35].

Evidence suggests that tumors create a variety of immunosuppressive substances that affect the host's immunity locally or systemically [36]. Patients having a detectable lymphocyte-mediated immune response to tumor-associated antigen had more aggressive features [37] but a great prognosis [38].

## Conclusion:

Strong relationship between hormonal and Her2/neu status of BC and TILs density. High TILs density has favorable outcome regarding OS and PFS, particularly in TNBC in metastatic cases with promising role of immunotherapy in these cases.

**List of abbreviations**

| | |
|---|---|
| AC | Adriamycin and cyclophosphamide |
| BOR | best overall response rate |
| BC | Breast cancer |
| CR | complete response |
| CRi | complete response indeterminate |
| CT | Computed tomography |
| FAC | flurouracil, Adriamycin and cyclophosphamide |
| FEC | flurouracil,Epirubcin and cyclophosphamide |
| ER | Estrogen receptor |
| HER2 /neu | Human epidermal growth factor 2 |
| H&E | Hematoxylin and eosin staining |
| HR | Hormonal receptor |
| LPBC | Lymphocytic predominant breast cancer |
| LTBC | Lymphocyte-trivial BC |
| NK cells | Natural killer cells |
| MRI | Magnetic resonance imaging |
| OS | Overall survival |
| PFS | Progression free survival |
| PR | Progestin receptor |
| PR | Partial response |
| TILs | Tumor infiltrating lymphocytes |
| TNBC | Triple negative breast cancer |

**Author contributions**

CONCEPTION: AG Gabr and AM Sayed.
LAB WORK: MT Hussien.
INTERPRETATION OR ANALYSIS OF DATA: AG Gabr, MT Hussien.
PREPARATION OF THE MANUSCRIPT: AG Gabr, AM Hefni and AM Sayed, MT Hussien and AZ Abdalla.
REVISION FOR IMPORTANT INTELLECTUAL CONTENT: AG Gabr, AZ Abdalla, MT Hussien and AM Sayed.
SUPERVISION: AM Hefni, MT Hussien, AG Gabr and AZ Abdalla.

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