Pharmacogn J. 2023; 15(6): 1185-1188
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Research Article

Correlation of Tumor Infiltrating Lymphocytes (TILs) to Apoptotic Index (AI) in Breast Cancer

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ABSTRACT

Background: TILs is higher in breast cancer tissue, especially in the stroma compared to normal breast tissue. There is still no research on the relationship between AI and TILS in breast cancer. Yet another study indicating the presence of lymphocytic infiltration was investigated further by detailed analysis of apoptotic epithelial/tumor cells, using the CytoDEATH M30 antibody. The number of apoptosis was significantly higher. **Methods:** This study used an observational analytic design with a cross-sectional approach to analyze the relationship between Tumor infiltrating lymphocytes (TILs) and the apoptotic index (AI) in breast cancer. This research was conducted at H. Adam Malik General Hospital. The study was conducted using a case series model to see the correlation between Tumor Infiltrating Lymphocytes (TILs) and Apoptotic index (AI) in Breast Cancer. **Results:** In this study there were 52 patients where the mean age was 54.8 years with a standard deviation of 9.66 years Based on the characteristics of the TNM, it was found that most of the patients came with T3 (24 patients/46.2%), N0 (29 patients/55.8%) and M1 (31 patients/59.6%). Based on the frequency, there were 35 patients with high TILS or 67.3% of the total sample and 44 patients with high AI or 84.6%. In this study, an analysis of the relationship between TILS and AI was carried out where a p value <0.001 was obtained indicating a significance and relationship between TILS and AI. **Conclusions:** There is a significant relationship between tumor infiltrating lymphocytes (TILs) and the Apoptotic index (AI).

Key words: Apoptotic Index, Breast Cancer, H. Adam Malik General Hospital, Tumor Infiltrating Lymphocytes.

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History

- Submission Date: 29-09-2023;
- Review completed: 04-11-2023;
- Accepted Date: 07-11-2023.

DOI : 10.5530/pj.2023.15.215

Article Available online

http://www.phcogj.com/v15/i6

INTRODUCTION

TILs, or tumor-infiltrating lymphocytes, are lymphocytes that either surround or actively combat cancer cells. Tumor Infiltrating Lymphocytes (TILs) have been linked in a number of studies to the advancement of many cancers as well as patient survival, including ovarian, bladder, colon, prostate, rectum, lung, melanoma, and breast cancers. It has been noted that as compared to normal breast tissue, breast cancer tissue has a larger concentration of TILs, particularly in the stroma. Because chemotherapy treatments are more effective when applied to immunocompetent tumors, the overall survival and prognosis of breast cancer patients are improved when TILs are present.[1]

A tumor's apoptotic index, or AI, is a measurement of how many cancer cells are dying there. The ratio of apoptotic or dying cells to 100 cancer cells is used to estimate this. Cancer cells are those that divide uncontrolled due to a failure to regulate apoptosis. Inhibition of anoikis, a form of apoptosis that often prevents the escape of cells from the extracellular matrix, also aids in the metastatic process.[2] An indicator and prognostic factor for malignancies is the evaluation of the apoptosis index. Using the Haematoxylin & Eosin and Terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling test techniques, AI was evaluated visually and biochemically.[3]

The connection between AI and TILS in breast cancer is currently unexplored. Another study that revealed lymphocytic infiltration was examined in further depth utilizing the CytoDEATH M30 antibody on apoptotic epithelial/tumor cells. There were noticeably more apoptosis cases.[4] In the case of non-small cell lung carcinoma, the number of apoptotic cells was significantly higher in tumors with high numbers of CD3+ and CD8+ lymphocytes (p=0.01) and B cells (p=0.05).10 Other studies also demonstrated a significant positive correlation between the degree of CD8+ TILs and the occurrence of apoptosis in cases of hepatocellular carcinoma detected in this study.[5]

METHODS

This study used an observational analytic design with a cross-sectional approach to analyze the relationship between infiltrating lymphocytes (TILs) and the apoptotic index (AI) in breast cancer. This research was conducted at H. Adam Malik General Hospital. The study was conducted using a case series model to see the correlation between Infiltrating Lymphocytes (TILs) and Apoptotic index (AI) in Breast Cancer.

The data that has been collected is processed, and analyzed through statistics and presented in tabular form. Data were analyzed using Fisher's exact test which was processed using a computer program. Data will be entered into a 2 x 2 table for each independent variable, namely tumor infiltrating lymphocytes (TILs) with high and low categories. The dependent variable is the Apoptotic Index (AI) with high and low categories. This study uses a 95% confidence interval and is stated to be statistically significant if the p value <0.05.

Cite this article: Siregar KB, Siregar BW, Suyatno. Correlation of Tumor Infiltrating Lymphocytes (TILs) to Apoptotic Index (AI) in Breast Cancer. Pharmacogn J. 2023;15(6): 1185-1188.

RESULTS

In this study there were 52 patients where the mean age was 54.8 years with a standard deviation of 9.66 years. The median value is 54.5 years with the youngest age being 29 years and the oldest being 78 years. Based on the characteristics of the TNM, it was found that most of the patients came with T3 (24 patients/46.2%), N0 (29 patients/55.8%) and M1 (31 patients/59.6%). It was found that the most patient stage was stage IV or 26 patients (50%) and it was found that most of the patients came with histopathological characteristics of IDC, namely 29 patients (55.8%) Table 1.

Based on the frequency, there were 35 patients with high TILS or 67.3% of the total sample and 44 patients with high AI or 84.6%. This is shown in table 2.

In this study, an analysis of the relationship between TILS and AI was carried out where a p value <0.001 was obtained indicating a significance and relationship between TILS and AI. This is shown in table 3.

DISCUSSION

The research subjects' average age was 54.82 ± 9.66 years. These findings are consistent with research by Silva et al. from Tzhun 2021, which found the average age to be 50.5 years (standard deviation, SD 10.7).[6] The average age of patients was 54.2 ± 12.8 years (range 29 to 84, median 52, IQR 45-65). Kamal Basri Siregar's study on TNBC patients found the median age to be 46 years, with the youngest being 27 years and the oldest being 73 years. Age-wise, the incidence of breast cancer generally rises until the menopausal years (about 50–55 years), then declines until it starts to rise again beyond 60 years of age.[7]

Based on clinical and demographicid factors, it was discovered that most patients had IDC histological classification and that most patients had stage IV T3, N0, and M1 histopathological classifications. In contrast to Deici *et al*. 2018, wherein more than 60% of cases are classified as stage 2 ,[5] research by Silva et al. tzhun 2021 found that 143 cases (83.6%) were clinical stage III [6]. Fares et al. also obtained IDC; of these, fifty-seven patients (37.5%) had grade III disease.[8]

This is marginally different from the findings of Kamal Basri Siregar's study, which indicated a prevalence of cancer in 33 individuals (55%) with T4 sizes and 27 individuals (45%) with T3 sizes. The study by Kamal Basri Siregar did not include any T1 or T2 patients. This may have occurred as a result of Siregar's research, which concentrated on TNBC and had a tendency to be more aggressive. Histopathology confirms this, as does the research of Kamal Basri Siregar, who demonstrated that in H. The majority of TNBC patients at Adam Malik General Hospital had invasive ductal carcinoma (20%), accounting for 48 patients. Of those who underwent response assessment, 48% responded to chemotherapy and 52% did not respond to neoadjuvant treatment. Neoadjuvant.11 This is due to the fact that, as can be shown from the fundamental features of the variables in this study, the majority of cancer diagnoses have progressed to an advanced level (stage III–IV).[7]

Pujadi *et al*. from 2020, which found that infiltrating ductal carcinoma (IDC) accounted for more than 90% of cases of breast carcinoma, with medullary carcinoma accounting for about 5% of cases.[9] Fares *et al*. also found that IDC (invasive ductal carcinoma) was the most common histopathological type (73.9%).[8] This is in contrast to Silva *et al*.'s 2021 study, which found that invasive ductal carcinoma was not detail (NOS) was the most common histology in 160 cases (93.6%).[12] Malignant cells attach themselves to the fibrous stroma, causing it to become viscous fluid. The tumor penetrates the breast tissue and enters the lymphatic and vascular systems, allowing it to reach the systemic circulation and localized nodes (axillary and occasionally internal mammary). Tumor behavior prediction and three features (nuclear pleomorphism, tubule development, and mitotic frequency) were used to determine the histological grade of the tumor.16 This type frequently metastasizes to the brain, liver, lungs, or bones.[6]

There were 65.7% of participants in this study who had high TILS. TILs are crucial markers of the immunological milieu surrounding tumors. High TIL tumors are linked to higher grades and are intimately linked to elevated PD-L1 expression. There were 27 patients with locally advanced breast cancer who had high TILs and 38 individuals with intermediate TILs in the Caziuc et al. 2019 study.[10]

TILs, or tumor-infiltrating lymphocytes, are lymphocytes that either surround or actively combat cancer cells. Tumor Infiltrating Lymphocytes (TILs) have been linked in a number of studies to the advancement of many cancers as well as patient survival, including ovarian, bladder, colon, prostate, rectum, lung, melanoma, and breast cancers. It has been noted that as compared to normal breast tissue, breast cancer tissue has a larger concentration of TILs, particularly in the stroma. Overall, the presence of TILs in breast cancer improves survival and prognosis because immunocompetent tumors respond better to chemotherapeutic drugs.[11]

Table 1: Sample characteristics and TNM study sample.

Parameters	Value
Age, years	
Mean ± SD	54,82 ± 9,66
Median (min-max)	54,5 (29-78)
T, n (%)	
T1	12 (23,1%)
T2	4 (7,7%)
T3	24 (46,2%)
T4	12 (23,1%)
N, n (%)	
N0	29 (55,8%)
N1	23 (44,2%)
M, n (%)	
M0	21 (40,4%)
M1	31 (59,6%)
Stadium, n (%)	
I	0 (0%)
IIA	5 (9,6%)
IIB	0 (0%)
IIIA	0 (0%)
IIIB	21 (40,4%)
IV	26 (50%)
Histopathological Classification, n (%)	
IDC	29 (55,8%)
ILC	23 (44,2%)
Total	52 (100%)

Table 2: TILS and AI frequency distribution.

Parameters	Value
TILS, n (%)	
Low	35 (67,3%)
High	17 (32,7%)
AI, n (%)	
Low	44 (84,6%)
High	8 (15,4%)
Total	52 (100%)

Table 3: Relationship between TILS and AI in breast cancer patients.

TILS	Apoptotic Index						p value*
	High		Low		Total		
	N	%	N	%	n	%	
High	35	100.0%	0	0.0%	35	100.0%	<0.001
Low	9	52.9%	8	47.1%	17	100.0%	

Inflammatory responses involving the innate and adaptive immune systems being coordinated are maintained and initiated by the human immune system. Tumor-killing immune responses can be triggered by expressing antigenic proteins, which are altered by neoplastic transformation. The infiltration of immune cells into regions where tumor cell proliferation takes place is typically observed in conjunction with malignant tumors. Although it is common to see immune cells infiltrating the tumor, the exact makeup of these cells varies widely according on the tumor type and the organ in question. The impact of lymphocyte infiltration on solid tumors is documented in a number of publications.[12,13]

One of the elements that significantly prevents the development of breast cancer is the immune system, or body immunity. The strong relationship between tumor regression and bodily immunity has gained particular attention recently. One of the body's cellular immune systems, lymphatic T cells, is crucial in slowing the development of breast cancer. Tumor infiltrating lymphocytes (TILs) are lymphocyte cells that migrate around tumors. They have emerged as a significant biological marker for breast cancer, particularly in its early stages. The expression or presence of TILs in breast cancer is linked to prognoses in HER2 and TNBC subtypes, which is important for the development of immunotherapy for breast cancer. The presence of TILs in breast cancer is consistently measurable, according to the International Tumor Infiltrating Lymphocytes (TILs) can be used as a prognostic and predictive factor in breast cancer as well as a routine and required step to be examined before giving therapy. By suppressing T cells, TIL production may offer a great deal of promise for developing immunotherapy (Tcell checkpoint inhibition). Increased TIL in primary tumors has significant prognostic and predictive value in breast cancer, especially in the TNBC and HER2 subtypes, according to several studies.[14] Hallmark of cancer goes into great detail about the significance of the immune system's role in controlling cancer cells and the development of targeted therapy. Multivariate analysis revealed high TIL expression as an independent predictive factor with pathological complete response (pCR), notably in the HER2 group.[15] A case-control study found that high TIL expression was linked to high grading, hormone receptor negative, and HER2 positive.

Previous research has demonstrated a relationship between immune markers and the way neoadjuvant chemotherapy works in breast cancer patients. The outcomes with adjuvant chemotherapy are similar. When TNBC and HER-2 are positive, these immune markers are typically strong.[16]

According to research by Kurozumi et al. from 2019, 32 patients out of all patients had low TIL expression.[24] Research by Angelico from 2021 revealed that moderate TIL expression was the most prevalent form, with an incidence of 49%. Actually, there is a strong correlation between high TILs expression and a better prognosis for locally progressed breast cancer.[17]

According to Asano *et al.*'s 2018 study, 81 patients (45.8%) and 96 (54.2%) patients belonged to the low TIL group. Tumor infiltrating lymphocytes (TILs), a regular pathological examination for many forms of solid cancer, are one predictor that has been thoroughly researched. TILs are indicators of the immune system's reaction to tumors. They are also a prognostic factor in a number of cancer types, including the ability to predict treatment response.[18] TILs can be used as a tool to evaluate the immune system's reactivity in a variety of cancer types, such as colon, ovarian, lung, bladder, breast, etc. The association between TIL expression and clinicopathology in triple negative breast cancer (TNBC) indicates that high TIL expression is linked to smaller tumor sizes but is not significantly related to grading or staging.[19]

84.6% of the participants in this study had a high apoptotic index. Kamal Basri Siregar's research, which revealed a majority of patients with an elevated apoptotic index of 51.7%, is not distant from this study. The term "apoptotic index" (AI) refers to the rate at which cancer cells in a tumor die.[7] The ratio of apoptotic or dying cells to 100 cancer cells is used to estimate this. Cancer cells are those that divide uncontrolled due to a failure to regulate apoptosis. Inhibition of anoikis, a kind of apoptosis that often prevents cell escape from the extracellular matrix, also aids in the metastatic process. Evaluation of the apoptotic index in malignancies serves as a predictive and prognostic factor.[2]

TILS and AI were found to positively correlate in this study. A thorough examination of apoptotic epithelial/tumor cells was conducted to further analyze other studies that indicated the presence of lymphocytic infiltration. The amount of apoptosis was noticeably greater.[4]

This is consistent with the idea explaining how TILs can trigger AI. The primary biological constituents of the immune-active tumor microenvironment, which are represented by T cells, B cells, natural killer (NK) cells, and dendritic cells, are known as tumor infiltrating lymphocytes, or TILs. The exact process by which TIL interacts with tumor cells is unknown, although apoptosis induction is one potential approach. If the primary biological effector mechanism underlying the cytotoxic impact of TIL is apoptosis. Numerous investigations have demonstrated that TIL-induced tumor cell death involves three primary pathways: ligands (FasL/Fas), granule exocytosis (perforin and GrB), and cytotoxic T lymphocytes (CTL) that secrete TNF-α and IFN-γ, which are thought to be indicative of the host immune activating response. Thus, a connection exists between TILs and AI.[20]

T cells, B cells, and NK cells make up TIL; in breast cancers, these cell types account for roughly 75%, 20%, and 5% of TIL, respectively. (1) Naive CD8+ T lymphocytes become activated upon attaching to dendritic cells (DC) in the lymph nodes, which is how TIL affects apoptosis. After activation, CD8+ effector T lymphocytes identify and attach to tumor cells, releasing granzymes to cause apoptosis. (2) Regulatory T cells bind CTLA-4 to CD80/86 on DCs to limit DC activity and dampen antitumor immune responses by secreting immunosuppressive cytokines. (3) NK cells identify tumor cells as "foreign," attach to them, release granzymes into the cells, and secrete immunostimulatory cytokines that draw CD8+ effector T cells into the tumor microenvironment (TME). (4) B cells can secrete immunosuppressive cytokines like TGF-β, IL-10, and IL-35 that encourage tumor growth, but they can also secrete tumor antigen-specific IgG antibodies that, when bound to tumors, cause apoptosis.[16]

A strong positive association was also observed in other research between the level of CD8+ TILs and the incidence of apoptosis in hepatocellular carcinoma (HCC) cases that were identified in this investigation. The potential involvement of cytotoxic T cells in liver damage resulting from hepatitis B or C virus (HBV or HCV) infection is unclear. The study discovered that compared to HBV infection, the density of CD8+ T lymphocytes in the liver lobules with HCV infection was much higher.[21]

Additionally, in non-small cell lung cancer, tumors with high levels of B cells (p=0.05) and CD3+ and CD8+ lymphocytes (p=O.Ol) had a considerably larger number of apoptotic cells. By counting apoptotic cells and bodies from the same region as the mononuclear cell infiltrate, the apoptotic index (AI%) was calculated. For adenocarcinoma (AC) and squamous cell lung carcinoma (SQCC), the mean AI% was 1.10% (min 0.12%, max 5.33%) and 1.23% (min 0.030/0, max 6.09%), respectively.[3]

Conversely, research on non-seminomatous germ cell tumors in the testicles did not find any association between the quantity of TIL and AI. AI, or the proportion of apoptotic cells in all tumor cells under investigation, was used to compute the number of apoptosis. Since lymphocytes were thought to be incapable of inducing apoptosis in tumor cells, only those

lacking apoptotic characteristics were utilized to link Spearman's rank with apoptotic tumor cells. In the case of non-seminomatous germ cell tumors. TIL and AI do not correlate in tumor tissue, with the exception of the metastatic embryonal cell carcinoma subgroup.[20]

The limitation of this study is that it is a single-center study. Multi-center research may be able to explain this phenomenon more clearly so that the research power becomes stronger. Another limitation of this study is that it is a retrospective study. Prospective studies allow researchers to see first-hand clinical outcomes and obtain more objective demographic characteristics.

CONCLUSIONS

There were 35 patients with high TILS (67.3%) and 44 patients with high AI (84.6%). In the results of this study there is a significant relationship between tumor infiltrating lymphocytes (TILs) and the Apoptotic index (AI).

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHORS' CONTRIBUTIONS

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Research permission and approval were obtained from the Ethics Committee of the Faculty of Medicine, Universitas Sumatra Utara.

ACKNOWLEDGEMENT

None

CONFLICTS OF INTEREST

None

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Cite this article: Siregar KB, Siregar BW, Suyatno. Correlation of Tumor Infiltrating Lymphocytes (TILs) to Apoptotic Index (AI) in Breast Cancer. Pharmacogn J. 2023;15(6): 1185-1188.