Pharmacogn J. 2023; 15(6): 1181-1184
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Research Article

Correlation of Mitotic Index (MI) and Tumor Infiltrating Lymphocytes (TILs) to Chemotherapy Response in Triple Negative Breast Cancer (TNBC) at Haji Adam Malik General Hospital Medan

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ABSTRACT

Background: The response to chemotherapy depends on the proliferation of cancer cells. The higher the proliferation of cancer cells, the better the response. Mitotic Index and Tumor Infiltrating Lymphocytes are markers related to the rate of proliferation and cancer immunity. **Objectives:** to analyze the correlation of Mitotic Index (MI) and Tumor Infiltrating Lymphocytes (TILs) to chemotherapy response in Triple-negative breast cancer (TNBC). **Methods:** This study used an observational analytic design with a cross-sectional approach. It was conducted at the Division of Oncology Surgical, Department of Surgery, USU Medical Faculty, H. Adam Malik Hospital, Medan, for six months with a sample of 60 people. **Results:** On average, most respondents are 47 years old, with the youngest age being 27 and the oldest 73 years old. Most respondents have Grade II, with most in stage IIIB. There was no relationship between Tumor Infiltrating Lymphocytes and Chemotherapy Response (p>0.05), with a Positive Predictive Value (NPP) of 47% and a Negative Predictive Value (NPN) of 50%. **Conclusion:** There is no relationship between the mitotic index and clinical response to chemotherapy, and there is no relationship between tumor-infiltrating lymphocytes and the response to chemotherapy due to influencing factors such as albumin, T stage, menopausal status, and receptor status.

Key words: Mitotic index, Tumor-infiltrating lymphocytes, Chemotherapy response, TNBC.

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History

- Submission Date: 22-09-2023;
- Review completed: 30-10-2023;
- Accepted Date: 06-11-2023.

DOI : 10.5530/pj.2023.15.214

Article Available online

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

INTRODUCTION

Breast cancer is the most frequent cancer among women in developed nations, making it a major worldwide health concern. The World Health Organization (WHO) estimates that 8–9% of women will get breast cancer. The International Agency for Research on Cancer (IARC) reports that in 2012, there were 43.1 new instances of breast cancer for every 100,000 women, and 12.9 deaths for every 100,000 women.[1]

Ten out of every 10,000 Indonesians have breast cancer, and 70% of patients visit a doctor or hospital at an advanced stage, according to data from the Jakarta Breast Cancer Foundation. In Indonesia, a high staging rate for breast cancer patients is a result of inadequate public knowledge.[2] Based on data from the Hospital Information System (SIRS) in 2018, breast cancer ranks first (27/per 100,000 population) in inpatients throughout Indonesia, 21.69% of all cancer patients. In the surgical oncology subdivision of H. Adam Malik Hospital, the number of cases of breast malignancy recorded in 2012-2014 was 1,107.[3]

Invasive breast cancer is classified into multiple subtypes based on gene profiling, the presence or absence of hormone receptors such as human epidermal growth factor receptor 2 (HER2+/HER2-), progesterone receptor (PR+/PR-), and estrogen receptor (ER+/ER-). Triple-negative breast cancer (TNBC) is one of them.[4] One subtype of breast cancer known as triple-negative breast cancer (TNBC) is defined as having no expression of the human epidermal growth receptor (HER-2), progesterone receptor (PR), or estrogen receptor (ER). TNBC makes up 15–25% of all occurrences of breast cancer; Hispanic or African-American women are more likely to get TNBC, particularly if they are premenopausal (under 40 years old).[5]

One trait of cancer cells is their unchecked proliferation. One prognostic indicator that may be assessed by correlation at the cellular level, like mitosis, is the tumor growth rate. Therefore, the proliferation rate in neoplasms is determined by counting the number of mitotic cells (mitotic index / MI). High proliferation neoplasms typically have a dismal prognosis.[6] For a long time, researchers have examined this mitotic activity in relation to chemotherapy sensitivity and prognosis in patients with breast cancer.[7] Moreover, increased cell division will increase the likelihood of tumor recurrence and the potential for total tumor tissue reduction when cytotoxic neoadjuvant therapy is administered.[8]

TILs, or tumor-infiltrating lymphocytes, encircle or combat cancer cells. The association between tumor-infiltrating lymphocytes (TILs) and cancer progression and patient survival has been reported in a number of researches. These studies have included ovarian, bladder, colon, prostate, rectal, lung, melanoma, and breast malignancies. It has been noted that as compared to normal breast tissue, breast cancer tissue has a larger concentration of TILs, especially in the stroma. Because chemotherapy medications can more effectively target immunocompetent tumors, the overall survival and prognosis of breast cancer patients are improved when TILs are present.[9]

Cite this article: Siregar KB, Siregar BW, Suyatno. Correlation of Mitotic Index (MI) and Tumor Infiltrating Lymphocytes (TILs) to Chemotherapy Response in Triple Negative Breast Cancer (TNBC) at Haji Adam Malik General Hospital Medan. Pharmacogn J. 2023;15(6): 1181-1184.

The response to chemotherapy depends on the proliferation of cancer cells. The higher the proliferation of cancer cells, the better the response. MI and TILs are markers related to the rate of proliferation and cancer immunity. Therefore, there is a correlation between MI and TILs on chemotherapy response.[10,11] Chemotherapy response is a change that occurs in clinical tumor size before chemotherapy is given and after chemotherapy is given.[12] The classification used in this study is the RECIST guideline. This system has four primary assessments: Complete response, Partial response, Stable disease, and Progressive Disease.[13]

METHODS

In order to determine the relationship between the mitotic index (MI) and tumor infiltrating lymphocytes (TILs) and chemotherapy response in triple-negative breast cancer (TNBC), this study used an observational analytic methodology with a cross-sectional approach. The USU Medical Faculty, H. Adam Malik Hospital in Medan, is home to the Surgical Oncology Division of the Department of Surgery, where this study was carried out. Following the proposal's approval by the ethics committee, this study was carried out. The duration of this study will be six months.

The study's inclusion requirements included neoadjuvant chemotherapy, a histological grade evaluation, an immunohistochemistry examination, and breast cancer in women with triple-negative breast cancer (TNBC) subtypes. The study's exclusion criteria included sources of incomplete data. Patients with triple-negative breast cancer (TNBC) made up the study's population. On the other hand, all female patients with Triple-negative breast cancer (TNBC) who visited the Surgical Oncology Division of RSUP included the study's sample. H. Adam Malik satisfied the inclusion and exclusion criteria. He had immunohistochemical and histological investigations, as well as chemotherapy, between January 1, 2014, and December 31, 2019. There are sixty samples in total.

Data were gathered over a five-year period (January 1, 2014 – December 31, 2019) from medical records at H. Adam Malik Hospital in Medan. Data from medical records are gathered over the course of two to eight weeks. Age, gender, histology (cancer type, grade, MI, TILs), immunohistochemistry (subtype), and response to chemotherapy (positive or negative) were the data collected for this study. Tabular data is information that has been gathered, processed, analyzed using statistics, and presented.

The chi-square test was used to examine the data, and a computer program was used to analyzed the data. In the event that the data distribution fails to satisfy the chi-square test criteria, the Fisher exact test will be employed. For each independent variable, namely the mitotic index (MI) and tumor-infiltrating lymphocytes (TILs), data will be placed into a 2 x 2 table with high and low categories. Chemotherapy response, whether positive or negative, was the dependent variable. A p-value of less than 0.05 was considered statistically significant in this investigation, which employed a 95% confidence interval.

RESULTS

This study was followed by as many as 60 research subjects, characteristic of subject in Table 1, with the aim of research to determine the relationship between Mitotic Index and Tumor Infiltrating Lymphocytes on the response to chemotherapy in triple-negative breast cancer (TNBC) at HAM Hospital, presented in table 1. The majority of respondents are on average aged 47 years old, with the youngest age being 27 years old and the oldest being 73 years old. the pathological results of Invasive Ductal Carcinoma (IDC) and Invasive Lobular Carcinoma (ILC), with the majority of the results being IDC as many as 48 people, and followed by ILC results as many as 12 subjects. The majority of respondents had Grade II as many as 26 people, followed by Grading III as many as 25 people, and finally followed by Grading I as many as 9 people. Respondents in stage IIIB as many as 45 people followed by stage IIIA as many as 15 people. Mitotic index with a high score of 36 people followed by a low score of 24 people. High TIL value of 35 people followed by a low TIL value of 25 people.

Based on the Chemotherapy Response in this study, table 1 notes that it is said to be "Response" if the results of chemotherapy (Response and Partial Response) are said to be "Non-Response" if the results of chemotherapy (Non-Response and Progressive). With the majority of patients from 60 subjects, 31 people had "Non-Response," followed by "Response" as many as 29 people.

The results found that there was no relationship between the Mitotic index and the chemotherapy response in Table 2, analyzed using SPSS version 26 with the chi Square Test (p>0.05), with a Positive Predictive Value (NPP) of 45% and a Negative Predictive Value (NPN). 52%, so the Mitotic Index cannot be used to predict the clinical response to chemotherapy.

The resulting relationship between tumor-infiltrating lymphocytes and chemotherapy in Table 3, analyzed using the chi-square test, the results found that there was no relationship between Tumor Infiltrating Lymphocytes and Chemotherapy Response (p>0.05), with a Positive Predictive Value (NPP) of 47% and a Negative Predictive Value (NPN) 50%. Thus, TIL cannot be used to predict clinical response to chemotherapy.

Table 1: Characteristics of research subjects.

Characteristics	Frequency	Percentage	mean ± SD	Median (min-max)
Age	60	100	47.18 ±11.23	45.50 (27-73)
Pathology results				
IDC	48	80		
LIC	12	20		
Grading				
I	9	15		
II	26	43		
III	25	41		
Stadium				
IIIA	15	25		
IIIB	45	75		
Mitotic Index				
Tall	36	60		
Low	24	40		
TILs				
IIIA	35	58.3		
IIIB	25	41.7		
Chemotherapy Response				
Response	29	48.3		
Non-Response	31	51.7		

IDC: Invasive Ductal Carcinoma; ILC: Invasive Lobular Carcinoma; TILs: Tumor Infiltrating Lymphocytes; SD: **Standard Deviation**

Table 2: The relationship between mitotic index and chemotherapy response.

MI	Chemotherapy Response						p-value
	R		NR		Total		
High	16	45.7%	19	54.3%	35	100.0%	0.414
Low	13	52.0%	12	48.0%	25	100.0%	

Table 3: Relationship between tumor infiltrating lymphocytes and chemotherapy response.

TIL	Chemotherapy Response						p-value
	R		NR		Total		
High	17	47.2%	19	52.8%	35	100.0%	0.521
low	12	50.0%	12	50.0%	25	100.0%	

DISCUSSION

The study subjects 60 patients with TNBC, with characteristic data in Table 1. With the youngest respondent being 27 and the oldest being 73, the average age of the respondents is 47. In a prior study, 7739 individuals with a mean age of 59.5 years who were diagnosed with T1N0M0 TNBC between 2010 and 2015 and had breast cancer surgery were studied.[14] In a different study, the mean age at diagnosis for TNBC was 46.26 ± 12.22 years, whereas the mean age for all breast cancers was 52.90 ± 9.78 years ($p < 0.001$). Less than 50 years of age was shown to represent the majority of TNBC patients. Merely 278 (34.11%) patients with TNBC were over 50 years old, whereas 537 (66.88%) patients were under that age.[15] A study carried out at the Women's College Hospital and University in Toronto, Canada, found that the median age of presentation was 53 years old and that the frequency was 11.2%.[16]

TNBC is a clinically challenging strain because it is more common in women younger than 50, African-American women, oral contraceptive use > one year, carriers of the BRCA-I mutation, and women in low socioeconomic groups. Together with these factors, TNBC has an aggressive histological profile, a poor prognosis, a high mitotic grade, a large tumor size, and an aggressive expression profile with high p53 and ki67 expression but low bcl-2 expression, which results in lower relapse-free survival (RFS), overall survival (OS), and breast cancer-specific survival (BCSS).[15]

In India, the median age at which breast cancer is first detected is less than 50 years old, which is lower than in developed nations. Eighty percent of the patients are younger than 65. About 70% of them have advanced clinical stages at presentation, and they are frequently detected later.[17] According to published research, the prevalence of TNBC in India ranges from 27% to 35%, with an approximate value of 31%. This estimate is comparable to the African-American population, with nearly twice as many white women affected. Given that TNBC is one of the most aggressive subtypes of breast cancer, its high incidence could be a factor in India's high breast cancer patient death rate.[18]

TNBC is more common in African-American women, women under 50, women who have used oral contraceptives for more than a year, carriers of the BRCA-I mutation, and women from lower socioeconomic backgrounds, it presents clinical challenges. With a poor prognosis, high mitotic grade, big tumor size, and an aggressive expression profile that includes high p53 and ki67 expression but low bcl-2 expression, TNBC has an aggressive histology profile and a lower overall survival rate.[19]

A previous study on breast cancer in Indonesia with a large sample (247 patients) reported that the average age of TNBC patients was 51.84 years, almost the same as the results of this study.[20] According to a study conducted on TNBC patients at the Institute of Oncology Ljubljana, the majority of patients (60.3%) had already entered the postmenopausal phase. The median age of TNBC patients was 55.3 years.[21] A study conducted at Busan Paik Hospital revealed similar findings, indicating that 54 was the median age of TNBC patients. Over 20% of TNBC cases are in older people.[22] Five decades was the median age for both TNBC and non-TNBC subtypes, according to a Malaysian study.[23]

TNBC was more likely to develop in individuals who were younger, with a mean age of 49.4 and a median age of 48 years respectively in Malaysia.[24] Several studies in Kuwait and India also showed similar results, with the median age of TNBC patients being 48 and 46.12 years.[25] According to this study, out of 60 participants, the majority of respondents had as many as 26 Grade II individuals, as many as 25 Grade III individuals, and as many as 9 Grade I individuals. Additionally, there are just two stages: IIIA and IIIB. The majority of responders are in Stage IB, which has up to 45 participants, and Stage IIIA, which has up to 15 participants. The majority of TNBC cases with and without lymph node metastases (89.3% and 82.1%) had histological grades III. Dewi & Co. Only 66.7% of the 30 samples in the study had histological grade III, although more of the tumors (72.7%) had sizes greater than 50 mm.[26]

Stage II participants were more likely to have the basal-like TNBC subtype, but stage III subjects were more likely to have non-basal-like subtypes. In this study, stage IV TNBC basal-like participants had liver and bone metastases, while non-basal subjects only had lung and bone metastases. This result contrasts with a Japanese cohort study that reported brain and lung metastases associated with the basal-like subtype of TNBC. A second investigation verified the presence of brain metastases in TNBC basal-like subtype and TNBC linked to BRCA1 mutations. The metastatic potential of basal-like TNBC was lower in liver and bone than that of stage III non-basal subtype ductal carcinoma.[5]

In terms of pathological characteristics, 72% of the study population had grade III tumors at diagnosis, and 52% of the study population had stages III–IV. When compared to other research conducted in various geographic contexts, these values are higher. 30.1% of TNBC cases in India, according to Sarin *et al.*, had stage III–IV at diagnosis, whereas 35% of Chinese patients, according to Li et al., had histological grade III at diagnosis. According to a population-based study conducted in the United States, 75% of TNBC patients had histological grade III upon diagnosis, and 22% of patients presented with stages III–IV.[27,28]

In comparison to non-TNBC patients, TNBC patients are typically younger—less than 40 years old. Regarding age, a different study revealed a statistically significant association (p-value <0.001). TNBC is more frequent in premenopausal women and manifests sooner in life than other subtypes of breast cancer. Research indicates that people with TNBC typically receive their diagnosis 5–10 years younger than those without TNBC. In the study, premenopausal status ranged from 70% in Turkey, 48% in Lebanon, and 61% in TNBC patients.[14,29,30]

CONCLUSIONS

In the results of the study, there was no relationship between the mitotic index and the clinical response to chemotherapy ($p>0.05$), with NPP 45% and NPN% 52%. In this study, there was no relationship between tumor-infiltrating lymphocytes and the response to chemotherapy ($p>0.05$), with NPP 47% and NPN 50%. The results of this study are expected to be continued to examine the reasons or factors for the bias obtained in this study and what things affect the response to chemotherapy.

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 Mitotic Index (MI) and Tumor Infiltrating Lymphocytes (TILs) to Chemotherapy Response in Triple Negative Breast Cancer (TNBC) at Haji Adam Malik General Hospital Medan. Pharmacogn J. 2023;15(6): 1181-1184.