SJS SRIWIJAYA JOURNAL OF SURGERY

Sriwijaya Journal of Surgery Volume 4, Issue 2, Page No: 323 - 338
Available online: www.sriwijayasurgery.com
SJS 4(2): 323 - 338

Accuracy of a Novel Scoring System for Prediction of Response to Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer Patients

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Abstract

Background: Neoadjuvant chemotherapy (NAC) has become a widely accepted treatment option for locally advanced breast cancer (LABC). Furthermore, response to NAC is considered to be a predictor of favorable outcomes. It is known that some predictors are associated with NAC response.

Objectives: To assess the accuracy of scoring system for prediction of response to neoadjuvant chemotherapy in LABC.

Methods: Medical record of 50 patients received NAC at Mohammad Hoesin Hospital were retrospectively analysed between July 2019 to July 2020. Response of NAC in LABC was determined with Response Evaluation Criteria in Solid Tumours (RECIST). Variables of the scoring system are risk factors of breast cancer, immunohistochemical subtype, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ ratio, and neutrophil to lymphocyte ratio.

Results: A total of 50 patients with LABC received and completed NAC. The mean age was 48.2 ± 11.0 at the time of diagnosis. Good response to NAC was achieved in 38 patients (76.0%). This scoring system shows a sensitivity of 77.8%, a specificity of 83.3%, a positive predictive value of 18.4%, and a negative

predictive value of 24.4% with the Youden index of 66.1. The combination between less than three parity and positive estrogen receptor demonstrated better accuracy with a sensitivity of 96.3% and specificity of 77.7% and Youden index 74.

Conclusion: This pilot study suggests that this scoring system is potentially useful for predicting response to neoadjuvant chemotherapy in LABC patients and warrants further investigation in a larger population to validate this finding.

Keywords: breast cancer, scoring system, neoadjuvant chemotherapy response

1. Introduction

Based on GLOBOCAN 2012, there were approximately 14.1 million new cancer cases and 8.2 million cancer deaths, while in 2008 there were 12.7 million new cases and 7.6 million deaths. Breast cancer is the second most common cancer in the world, it is also a type of cancer that is often diagnosed in women in 140 out of 184 countries. Breast cancer is the most common cause of death in women with cancer (522,000 deaths in 2012). This data shows an increase of more than 20% of cases compared to the estimate in 2008.[1] Cancer until now has become a health problem in the world, including Indonesia.[2] Breast cancer usually occurs because of the interaction between genetic factors and environmental factors.[3] Some of the risk factors for breast cancer include genetic or hereditary factors, a family history of having had breast cancer, a history of having had a benign breast tumor or before. breast cancer, factors of early menstruation (age under 12 years) and menopause over the age of 50 years and a history of reproduction such as childlessness and not breastfeeding, childbirth for the first child over the age of 35 years, use of hormonal contraceptives> 7 years, history of radiation During breast growth, consume foods that are high in saturated fat, as well as alcoholic beverages.[4] A high body mass index (BMI) in patients receiving neoadjuvant chemotherapy is associated with a low pathologic complete response (pCR).[5,6] The neutrophil-lymphocyte ratio value before administration of neoadjuvant chemotherapy is a predictor of complete pathological response, as well as a significant prognosis for recurrence.[7] The pioneers of the invasive breast cancer molecular classification were Perou and Sorlie who identified 5 subtypes of invasive breast cancer, namely

Luminal A, Luminal B, normal breasts such as HER2 overexpression and basal like carcinoma, with different clinical results and different responses to neoadjuvant chemotherapy.[8]

In breast cancer, intratumoral cytotoxic CD8 + T cell infiltration is closely associated with long-term survival of the patient and good response to chemotherapy. Mao et al said it was reported that CD8 + lymphocytes are the main cells that are effective in the immune response, which shows better disease-free survival (DFS) in breast cancer patients.[9] Al Saleh et al, in their study it was reported that high CD8 + expression was predictable. Significant complete pathologic response after neoadjuvant chemotherapy and is a prognostic factor independent of Overall Survival (OS).[10] According to Seo et al., CD8 + is an important component of Tumor Infiltrating Lymphocytes (TIL) associated with chemotherapy response and can be used as a predictor of response to anthracyclines or anthracyclines / taxa based on breast cancer.[11] CD4 + levels serve as the basis of the immune system cytotoxic T lymphocytes. CD4 + T helper cells have an important role in modulating the immune system, especially maintaining long-term anti-tumor effects.

Given the existence of various factors that act as predictors of response to neoadjuvant chemotherapy in locally advanced breast cancer, the researchers wanted to assess these factors as a single scoring system, which is expected to provide a more meaningful value in predicting the response to neoadjuvant chemotherapy.

2. Methods

This type of research is a prognostic test for the accuracy of various risk factors (patient age, age at menarche, past or menopause, history of hormonal contraception, age at first pregnancy, parity, family history, and nutritional status), immunohistochemistry subtypes, CD4 + serum, CD8 + serum, serum CD4 + / CD8 + ratio, and neutrophil-lymphocyte ratio as a scoring system used to predict the response of neoadjuvant chemotherapy in patients with locally advanced breast cancer. This research was conducted in the surgical oncology polyclinic and inpatient installation of Dr. Mohammad Hoesin Hospital Palembang. The study period was from 01 July 2019 to 31 July 2020. The study population was patients with locally advanced breast cancer who received neoadjuvant chemotherapy at Dr. Muhammad Hoesin Hospital Palembang. The inclusion criteria in this study were patients with locally advanced breast cancer who were determined based on the criteria of the American Joint Committee of Cancer, underwent neoadjuvant chemotherapy, had a Karnofsky index ≥ 50, were willing to participate in the study and signed an informed

consent. The exclusion criteria in this study were patients who had previously undergone chemotherapy and immunocompromised patients.

3. Results

There were 50 samples obtained at the surgical oncology polyclinic and the inpatient installation of Dr. Mohammad Hoesin Hospital Palembang from 01 July 2019 to 31 July 2020 who met the inclusion and exclusion criteria. Overall, it was found that 38 patients (76.0%) showed a good response to neoadjuvant chemotherapy. Patient ages ranged from 30 to 67 years with a mean of 48.2 ± 11.0 years. There was no difference in patient age between groups with good and bad response to neoadjuvant chemotherapy ($p = 0.166$). The mean age of menarche of all study samples was 13.22 ± 1.4 years, there was no difference between the two groups ($p = 0.757$). A total of 22 (44.0%) patients had already experienced menopause while 28 (56.0%) had not yet experienced menopause. There was no association between menopause and response to neoadjuvant chemotherapy ($p = 0.852$). Most of the patients (66.0%) had a history of using hormonal contraceptives, but there was no significant relationship between family planning history and response to neoadjuvant chemotherapy in this study ($p = 0.520$). In the group with a good response to neoadjuvant chemotherapy, the mean age at first pregnancy was 23.9 ± 4.6 years, while in the group with a poor response it was 22.5 ± 7.4 years. The age at first pregnancy among patients did not differ between the two groups ($p = 0.423$). Twenty-five (92.6%) patients with parity <3 had a good response to neoadjuvant chemotherapy. In patients with parity ≥ 3, most of the patients (56.5%) responded well and there was a significant relationship between parity and response to neoadjuvant chemotherapy ($p = 0.003$).

Table 1. The relationship between the characteristics of the research subject and the chemotherapy response

Variable	Chemotherapy Response		p_Value
	Good	Bad	
Patient's Age	47.0 ± 10.6	52.1 ± 12.0	0.166*
Age of Menarche	13.18 ± 1.392	13.33 ± 1.614	0.757*
Menopause			
Yes	17 (77.3%)	5 (22.7%)	0.852**
No	21 (75.0%)	7 (25.0%)	
Hormonal contraceptives			
Yes	26 (78.8%)	7 (21.2%)	0.520**
No	12 (70.6%)	5 (29.4%)	
Age at first pregnancy	23.95 ± 4.626	22.50 ± 7.453	0.423*
Parity			
< 3	25 (92.6%)	2 (7.4%)	0.003***
≥ 3	13 (56.5%)	10 (43.5%)	
Family history of breast cancer			
Yes	12 (92.3%)	1 (7.7%)	0.110***
No	26 (70.3%)	11 (29.7%)	
Body Mass Index			
< 23	8 (80.0%)	2 (20.0%)	0.741***
≥ 23	30 (75.0%)	10 (25.0%)	

Note: *: Independent t-test, **: Chi-Square, ***Fisher's Exact, significant p<0.05

In the analysis with the chi-square test found a significant relationship between parity and cut off = 3 (p = 0.003) with OR = 9.6. This means that patients with parity <3 (0–2) are nearly 10 times more likely to show a good response to neoadjuvant chemotherapy than those with parity of 3 or more. To find the relationship between parity and response to neoadjuvant chemotherapy, an Area Under the Curve (AUC) analysis was performed. Parity was obtained with a cut-off point of 3, giving an AUC value of 0.698, a sensitivity of 83.3%, and a specificity of 64.8%, which means that parity <3 can be used as a predictor of response to neoadjuvant chemotherapy which is quite good at this research. Most of the patients (37 patients = 74.0%) had no family history of breast cancer, and only 13 patients (26.0%) had no family history of breast cancer. Statistical analysis did not find a significant relationship between family history of breast

cancer and response to neoadjuvant chemotherapy (p = 0.110). The patient's body mass index (BMI) ranged from 17.8 to 37.0 with a mean of 25.5 ± 3.7. Most of the patients (80%) with normal nutritional status had a good response. There was no significant relationship between the nutritional status of patients and the response to neoadjuvant chemotherapy (p = 0.741).

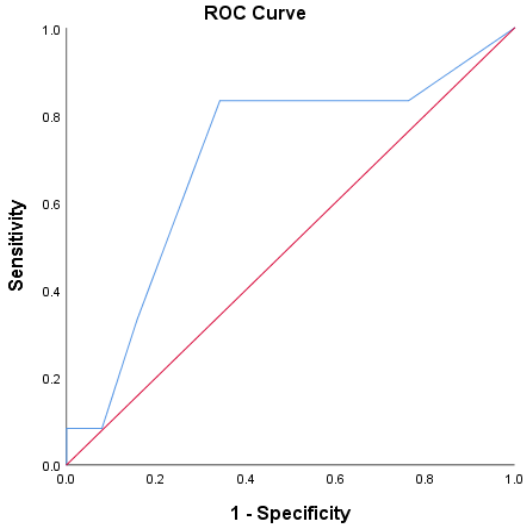

Figure 1. Results of AUC analysis of parity as a predictor of response to neoadjuvant chemotherapy

Biomarkers and chemotherapy response

There was also no association between immunohistochemistry subtypes and response to neoadjuvant chemotherapy (p = 0.827). Most of the patients (68.0%) had a positive ER expression, and 32% of the other patients had a negative ER expression. Among the patients with ER + it was found that 85.3% had a good response to neoadjuvant chemotherapy, while for patients with a good ER response was found only in 56.3% of cases. The difference in response to neoadjuvant chemotherapy was statistically significant (p = 0.025, OR = 4.5). Overall, the PR + expression was also found to be higher in 36 (72.0%) patients and only 14 (28.0%) with negative PR expression. However, statistical analysis found no association between PR expression and response to neoadjuvant chemotherapy (p = 0.637). There were 44 patients (88%) with HER2neu - expression, while overall only 6 patients (12%) had HER2neu + expression. The distribution of expression and its relationship with the response to neoadjuvant chemotherapy can be seen in the table below. Chi-square statistical test did not find a significant relationship between HER2neu expression and

response to neoadjuvant chemotherapy (p = 0.654). Of the total 50 samples of this study, there are 6 samples that do not have immunohistochemistry examination results for Ki67. When the Ki67 expression was distributed over the 20% limit, it was seen that 82.6% of cases with a Ki67 expression ≤ 20% had a good response to neoadjuvant chemotherapy, while for patients with a Ki67 expression> 20%, a good response was found in 66.7% of cases. However, there was no significant relationship between these two groups (p = 0.223).

Table 2. The relationship between biomarkers and the chemotherapy response

Variable	Chemotherapy Response		p_Value
	Good	Bad	
Immunohistochemistry subtype			0.827*
Luminal A	18 (81.8%)	4 (18.2%)	
Luminal B	14 (73.7%)	5 (26.3%)	
Her2neu	4 (66.7%)	2 (33.3%)	
Triple Negative	2 (66.7%)	1 (33.3%)	
Estrogen Receptor			0.025*
Positive	29 (85.3%)	5 (14.7%)	
Negative	9 (56.3%)	7 (43.8%)	
Progesterone Receptor			0.637**
Positive	28 (77.8%)	8 (22.2%)	
Negative	10 (71.4%)	4 (28.6%)	
Human Epithelial Receptor (HER2-Neu)			0.654**
Positive	4 (66.7%)	2 (33.3%)	
Negative	33 (75%)	11 (25%)	
Ki-67			0.223**
≤ 20%	19 (82.6%)	4 (17.4%)	
> 20%	14 (66.7%)	7 (33.3%)	

Note: *: Chi-Square, **Fisher's Exact, significant p<0.05

In this study, we want to see the relationship between several immunological parameters in serum, namely the number of CD4 +, CD8 +, CD4 + / CD8 + ratio, and Neutrophil Lymphocyte Ratio (NLR). Table 4.10 lists the average number and standard deviation of CD4 +, CD8 +, CD4 + / CD8 +, and NLR ratios. The results of statistical tests using unpaired t-test found no significant relationship between serum immunological parameters and the response to neoadjuvant chemotherapy ($p > 0.05$).

Table 3. The relationship between biomarkers and the chemotherapy response

Immunology Response	Chemotherapy Response		p_Value
	Good	Bad	
CD4+	856.97 ± 418.5	913.27 ± 432.29	0.689
CD8+	653.23 ± 373.5	4 (17.4%)	0.943
CD4+/CD8+ ratio	1.5 ± 0.8	7 (33.3%)	0.959
NLR	3.1 ± 2.1	2.9 ± 2.2	0.848

Note: *: Independent t-test, significant $p<0.05$

Determination of the score for each predictor

Predictors of menopause, history of hormonal contraception, family history, and immunohistochemistry subtypes (Luminal A, Luminal B, Triple negative, including ER, PR, HER2neu, and Ki67 expressions), were given scores of 1 and 2. For predictors with a numeric scale, namely, patient age, age at menarche, age at first pregnancy, parity, nutritional status, serum CD4 +, CD8 + serum, CD4 + / CD8 + ratio, and NLR, the cut-off point values were searched using the Area Under the Curve (AUC) analysis. Then for each sample is given a score of 1) if the predictor value is above the cut-off point and 2) if the value is below the cut-off point. Recapitulation of each predictor and the cut-off point value can be seen in Table 4 below.

Table 4. Determination of the score for each predictor

Predictor	Value			
	a	score	b	score
Patient's Age	< 41	1	≥ 41	2
Age of Menarche	≥ 12	1	< 12	2
Menopause	Yes	1	No	2
Hormonal Contraception	No	1	Yes	2
Age at first pregnancy	≤ 19	1	> 19	2
Parity	< 3	1	≥ 3	2
Family history of breast cancer	No	1	Yes	2
Body Mass Index	< 24	1	≥ 24	2
$CD4^+$ serum	≥ 1275	1	< 1275	2
$CD8^+$ serum	≥ 993	1	< 993	2
$CD4^+/CD8^+$ ratio	≥ 1,2	1	< 1,2	2
NLR	< 2	1	≥ 2	2
Luminal A	Positive	1	Negative	2
Luminal B	Positive	1	Negative	2
Triple negative	Negative	1	Positive	2
ER	Positive	1	Negative	2
PR	Positive	1	Negative	2
Her2neu	Negative	1	Positive	2
Ki67	Negative	1	Positive	2

In the Area Under the Curve (AUC) analysis, the cut-off point value of the total score was 25. In the validity test using the 2x2 table, sensitivity was 77.8%, specificity 83.3%, positive forecast value 18.4%, predictive value negative 24.4%, 22.2% false positive value, 75.6% false negative value, with a Youden index of 66.1.

Table 4. Validity test of the total score

Score	Chemotherapy Response		Total
	Good	Bad	
Score < 25	7	2	9
Score ≥ 25	31	10	41
Total	38	12	50

4. Discussion

Neoadjuvant chemotherapy is a therapeutic approach that is usually taken before operative therapy in cases of locally advanced breast cancer (stage IIIA - IIIC). The expected result is the occurrence of pathological Complete Response (pCR), which is the loss of all malignant cancer cells. Ideally clinical improvements are expected to facilitate surgery, improve overall survival (OS) and disease-free survival rate (DFS), and consider appropriate adjuvant chemotherapy protocols for patients.[12] However, complete pathological response (pCR) is only found at 10-25 % of patients. pCR is more common in patients who have small tumors, high grade tumors, tumors with ER-, and tumors with HER2neu overexpression.[13,14] Neoadjuvant chemotherapy results in pCRs of between 30-50% in HER2neu positive and triple negative breast cancer patients.[15] Response assessments can be done subjectively or objectively. Assessment of subjective response is difficult to assess because many factors influence, however, several factors that can be assessed include increased body weight or reduction of pain. This can help the doctor estimate an overall subjective response. Subjective responses can also be assessed through performance status. Assessment of objective response can be done by assessing the measured tumor diameter reduction through WHO criteria (bidimensional) or RECIST criteria (unidimensional) or using tumor markers such as CA 15-3.[16] In this study the response to neoadjuvant chemotherapy was assessed using the RECIST criteria.

In this study, evaluation of several factors, which theoretically can be used as a predictor of neoadjuvant chemotherapy response, derived from data that is always available or easily obtained, namely: age at diagnosis of breast cancer, age at menarche, menopause or not, history of use of hormonal contraceptives, age at first pregnancy, parity, family history of breast cancer, nutritional status, immunohistochemistry subtypes, expression of hormonal receptors ER, PR, HER2, Ki67 expression, CD4 + serum, CD8 + serum, serum CD4 + / CD8 + ratio, and NLR in the blood. Overall, there were 50 patients who were successfully evaluated. Of the 50 patients who were sampled in this study, it was found that 38 patients (76.0%) showed a good response to neoadjuvant chemotherapy and 12 patients (24.0%) showed a bad response. There was no significant difference between the two groups ($p = 0.166$).

Patient ages ranged from 30 to 67 years with a mean of 48.2 ± 11.0 years. Not much different from Yulianto et al's research in 2018 conducted at Abdul Wahab Sjahranie Hospital Samarinda, the age range of patients was 40-49 years. Suarta et al's study in 2015 also found that the mean age of patients was 44.5

± 7.9 years in 30 stage III breast cancer patients.[17] There was no significant relationship between age and response to neoadjuvant chemotherapy (p = 0.166).

Family history such as mothers, mother's sisters, siblings or siblings who have had breast cancer have a 4-6 times risk than those without risk factors.[4] In this study, most of the 37 patients (74%) were not known to have a history of breast cancer in the family, and only 13 patients (26%) had a family history of breast cancer. Statistical analysis did not find a significant relationship between family history of breast cancer and response to neoadjuvant chemotherapy (p = 0.110). In contrast to this study, Rahestyningtyas in 2019 found a significant relationship with a moderate correlation between a history of breast cancer and chemotherapy response. It was concluded that patients with a family history tended to have a poor response to neoadjuvant chemotherapy.[18]

In this study, the patient's body mass index (BMI) ranged from 17.8 to 37 with a mean of 25.5 ± 3.7. Most of the patients (80%) had over nutritional status and 20% had normal nutritional status. There was no significant relationship between the nutritional status of patients and the response to neoadjuvant chemotherapy (p = 0.741). Purwanto et al in 2015 found that excessive BMI and obesity can be at high risk of developing breast cancer, a similar study was also conducted by Fortner et al in 2020 and concluded the same thing. Excessive BMI or even obesity can increase leptin and chemokines in the body which in turn lead to various diseases, including the risk of breast cancer and poor response to chemotherapy.[19]

This study did not find a significant relationship between immunohistochemistry subtypes and response to neoadjuvant chemotherapy (p = 0.827). In line with Muhammad et al in 2020 who also did not find a significant relationship between immunohistochemistry and neoadjuvant chemotherapy response. Furthermore, in this study, statistical tests were carried out on each hormone receptor. Overall, there were more ER + and PR + than ER- and PR- and Her2neu - more than Her2neu +, which showed a good response to neoadjuvant chemotherapy. However, only the difference in response to neoadjuvant chemotherapy at ER hormone receptors was statistically significant in this study (p = 0.025, OR = 4.5).[20]

The distribution of results was similar to that of other researchers. Yulianto et al, patients with ER + were more than ER-, namely 93 (52.5%) patients, while ER- were 84 (47.5%) patients. There were 96 (54.2%) patients with PR +, which was greater than PR- that is, only in 81 (45.8%) patients. The majority of patients had negative HER2-neu, namely 109 (61.6%) patients and high Ki-67 with a range> 30%, there were 73 (41.2%) patients. In Suarta et al's study, positive ER was more dominant as much as 20 (76.7%),

positive PR by 18 (60%) and negative HER2neu by 10 (33.3%).[17] Pegah et al. In 2018 found lymphovascular invasion and hormone receptor positive is a highly accurate predictor of finding a good chemotherapy response.[12]

Another study in Ki67, Prihantono et al. In 2017 found that Ki67 had a strong positive correlation with neoadjuvant chemotherapy response, while Zhao et al found that Ki67 and HER2 could significantly predict disease free survival (DSF) and ER, PR, HER2-neu, Ki67 can predicted overall survival (OS).[21] In contrast to the results in this study, Ki67 did not have a significant relationship with response to neoadjuvant chemotherapy.

Several immunological parameters in this study, namely; serum CD4 + levels, serum CD8 + levels, serum CD4 + / CD8 + ratios, and NLR, with statistical tests using unpaired t-test, did not find a significant relationship between these immunological parameters and response to neoadjuvant chemotherapy ($p > 0.05$). This study is different from the research of Ghallab et al. In 2020 and Axelrod et al. In 2020, which found a significant relationship between CD8 + in chemotherapy response and FDS.[22,23]

Analysis with the chi-square test found a significant relationship between parity and response to neoadjuvant chemotherapy, with a cut-off point = 3 ($p = 0.003$) and OR = 9.6. This means that patients with parity <3 (0–2) are nearly 10 times more likely to show good response to neoadjuvant chemotherapy than those with parity of 3 or more. In line with this study, Muhammad et al. In 2020 also found a significant relationship between parity> 3 and response to neoadjuvant chemotherapy with an OR value of 10.8.[20] Fortner et al. In 2019 also found the same thing where parity ≥ 3 had a worse chemotherapy response compared to patients with parity <3. Parity at risk increases the risk of negative hormone receptors that can worsen the response to neoadjuvant chemotherapy.[19] Lee et al. in 2019 concluded that there was a significant relationship, with high correlation strength, between parity> 4 and chemotherapy response. There is a significant difference between patients with parous null and parity ≥ 2, where samples with parity ≥ 2 have a risk of experiencing poor chemotherapy response.[24]

Of all the factors that could theoretically be potential predictors of response to neoadjuvant chemotherapy in this study, only 2 factors were found that were statistically significantly related to the response to neoadjuvant chemotherapy, namely 1) ER expression and 2) Parity, with a cut-off point of 3. Accuracy of ER + combination, parity < 3 as a predictor of response to neoadjuvant chemotherapy is very sensitive and specific, with a sensitivity value of 96.3%, specificity of 77.7. The validity test of the ER +

combination, parity ≥ 3, obtained a sensitivity of 76.9% and a specificity of 70%, meaning that it is quite sensitive and specific. On the accuracy of the ER- combination, Parity < 3 is very specific with a predictive value of 100% success, with a sensitivity value of 66.7% and a specificity value of 100%. In this study, the calculation results of Youden Index obtained the highest value of accuracy at ER +, Parity <3 with a value of 74 and ER-, Parity <3 with a value of 66.7. This study is in line with Barlow et al who also found that parity ≥ 3, ER positive and negative can be used as predictors of response to neoadjuvant chemotherapy.[25]

The results of the development of the scoring system in this study, obtained the Youden index value of 66.1 with 19 variables used as predictors. In contrast to the results of this study, Hendry et al's study in 2017 recommended a neoadjuvant chemotherapy response scoring system in breast cancer from the biomarkers it made, namely immune response, invasive and ductal TILS, tumor metastase deposits and areas of tumor growth.[26] Krishnamurti et al. 2017 found high validity in triple-negative as a predictor of neoadjuvant chemotherapy response.[27]

5. Conclusion

There was no significant relationship between age at diagnosis of breast cancer, age at menarche, menopause or not, history of hormonal contraceptive use, age at first pregnancy, family history of breast cancer, nutritional status, immunohistochemistry subtypes, expression of PR hormonal receptors, HER2neu, Ki67, serum CD4 + levels, serum CD8 + levels, serum CD4 + / CD8 + ratios, and NLR in blood with neoadjuvant chemotherapy response, which can be used to predict the response to neoadjuvant chemotherapy in patients with locally advanced breast cancer at Dr. Mohammad Hoesin Hospital Palembang.

The combination of parity <3 and positive ER expression showed better accuracy with a sensitivity of 96.3%, a specificity of 77.7% and a Youden index of 74. The total predictor score for neoadjuvant chemotherapy response in this study had a sensitivity value of 77.8%, specificity of 83.3%. , the positive predictive value is 18.4%, the negative predictive value is 24.4%, the false positive value is 22.2%, and the false negative value is 75.6%, with a Youden index of 66.1.

6. References

1. International Agency For Research On Cancer, et al. Latest world cancer statistics Global cancer burden rises to 14.1 million new cases in 2012: Marked increase in breast cancers must be addressed. *World Health Organization*, 2013, 12. Diakses (5 desember 2019) melalui: https://www.iarc.fr/wp-content/uploads/2018/07/pr223_E.pdf
2. Ferlay, Jacques, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International journal of cancer*, 2015, 136.5: E359-E386.
3. Kabel, Ahmed M.; Baali, Fahad H. Breast cancer: insights into risk factors, pathogenesis, diagnosis and management. *Journal of Cancer Research and Treatment*, 2015, 3.2: 28-33. (6)
4. Direktorat Pengendalian Penyakit Tidak Menular. Pencegahan Kanker Payudara. Dalam: Buku Saku Pencegahan Kanker Leher Rahim & Kanker Payudara. Jakarta: Departemen Kesehatan Republik Indonesia; 2009. h. 11-13.
5. Egidio Del Fabro, et al. The Relationship Between Body Composition and Responseto Neoadjuvant Chemotherapy in Women with Operable Breast Cancer. The Oncologist, 2012;17:1240–1245
6. Josepmilly P, et al. Body mass index. A predictive factor in the pathological complete response. Opology Press. Cancer and Oncology: Open Access Journal
7. Chae, S., et al. Neutrophil–lymphocyte ratio predicts response to chemotherapy in triple-negative breast cancer. *Current oncology*, 2018, 25.2: e113.
8. Tang Ping; Tse, Gary M. Immunohistochemical surrogates for molecular classification of breast carcinoma: a 2015 update. *Archives of pathology & laboratory medicine*, 2016, 140.8: 806-814.
9. Mao, Yan, et al. The prognostic value of tumor-infiltrating lymphocytes in breast cancer: a systematic review and meta-analysis. *PloS one*, 2016, 11.4: e0152500.
10. Al-Saleh, Khalid, et al. Predictive and prognostic significance of CD8+ tumor-infiltrating lymphocytes in patients with luminal B/HER 2 negative breast cancer treated with neoadjuvant chemotherapy. *Oncology letters*, 2017, 14.1: 337-344.
11. Seo, A. N., et al. Tumour-infiltrating CD8+ lymphocytes as an independent predictive factor for pathological complete response to primary systemic therapy in breast cancer. *British journal of cancer*, 2013, 109.10: 2705-2713.

12. Pegah Sasanpour, Saleh Sanoughdaran, Alireza Mosavi-Jarrahi and Mon Malekzaadeh. Predictor of Pathological Complete Response to Neoadjuvan Chemotherapy in Iranian Breast Cancer Patients. Asian Pac J Cancer Prev. 2018; 19(9): 2423–2427. doi: 10.22034/APJCP.2018.19.9.2423 (59)
13. Khotimah S, Gondhowiardjo SA, Poetiray EC, Djoerban Z. Kemoradiasi Neoajuvan pada Kanker Payudara Lanjut Lokal. Radioterapi & Onkologi Indonesia. 2011; 2(1):1-4.
14. Lee HJ, Seo JY, Ahn JH, Ahn SH, Gong GY. Tumor-Associated Lymphocytes Predict Response to Neoadjuvant Chemotherapy in Breast Cancer Patients. J Breast Cancer. 2013; 16(1): 32-39.
15. Denkert C, Loibl S, Noske A, Roller M, Muller BM et al. Tumor-Associated Lymphocytes as an Independent Predictor of Response to Neoadjuvant Chemotherapy in Breast Cancer. J Clin Oncol. 2009; 28: 105-113
16. Purwanto H, Handojo D, Haryono SJ, Harahap WA, editor. Terapi Dalam: Panduan Penatalaksanaan Kanker Payudara. Jakarta: Perhimpunan Ahli Bedah Onkologi Indonesia; 2015.
17. Yulianto, Ade Yusuf; Irawiraman, Hadi; Ompusunggu, PMT Mangalindung. Gambaran Usia dan Stadium Klinis Pasien Kanker Payudara yang dilakukan Pemeriksaan Imunohistokimia di Rumah Sakit Abdul Wahab Sjahranie pada Tahun 2018. *Jurnal Kebidanan Mutiara Mahakam*, 2020, 8.2: 126-140.
18. Rahestyningtyas, Eccita, et al. Respon Kemoterapi Lini Kedua Gemcitabine Carboplatin Pada Pasin Kanker Ovarium Epitelial Rekuren di RSUD DR Soetomo Periode Januari 2015-Desember 2017. 2018. PhD Thesis. Fakultas Kedokteran.
19. Fortner, Renée T., et al. Parity, breastfeeding, and breast cancer risk by hormone receptor status and molecular phenotype: results from the Nurses' Health Studies. *Breast Cancer Research*, 2019, 21.1: 40.
20. Muhammad, Syamel, et al. Relationships between Histopathology Type and Neoadjuvant Chemotherapy Response for Cervical Cancer Stage IB2 and IIA2. *Open Access Macedonian Journal of Medical Sciences*, 2020, 8.B: 507-513.
21. Zhao, Yue, et al. Conversion of immunohistochemical markers and breast density are associated with pathological response and prognosis in very young breast cancer patients who fail to achieve a pathological complete response after neoadjuvant chemotherapy. *Cancer management and research*, 2019, 11: 5677.

22. Ghallab, Ahmed. Immune responses during neoadjuvant chemotherapy in triple negative breast cancer. *EXCLI Journal*, 2020, 19: 1295-1296.
23. Axelrod, Margaret L., et al. Changes in peripheral and local tumor immunity after neoadjuvant chemotherapy reshape clinical outcomes in patients with breast cancer. *Clinical Cancer Research*, 2020.
24. Lee, JungSun, et al. Parity Differently Affects the Breast Cancer Specific Survival from Ductal Carcinoma In Situ to Invasive Cancer: A Registry-Based Retrospective Study from Korea. *Breast cancer: basic and clinical research*, 2019, 13: 1178223418825134.
25. Barlow, William E., et al. Prospective breast cancer risk prediction model for women undergoing screening mammography. *Journal of the National Cancer Institute*, 2006, 98.17: 1204-1214
26. Hendry, Shona, et al. Assessing tumor infiltrating lymphocytes in solid tumors: A practical review for pathologists and proposal for a standardized method from the International Immuno-Oncology Biomarkers Working Group: Part 1: Assessing the host immune response, TILs in invasive breast carcinoma and ductal carcinoma in situ, metastatic tumor deposits and areas for further research. *Advances in anatomic pathology*, 2017, 24.5: 235.
27. Krishnamurti U, Wetherilt CS, Yang J, Peng L, Li X. Tumor-infiltrating lymphocytes are significantly associated with better overall survival and disease-free survival in triple-negative but not estrogen receptor–positive breast cancers. Human pathology. 2017 Jun 1;64:7-12.