Systemic Immune-Inflammation Index As Predictor Factor Of Neoadjuvant Chemotherapy Response In Locally Advanced Breast Cancer At Dr. Soetomo General Hospital

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ABSTRACT

Background: Breast cancer is the most prevalent malignancy and the leading cause of death among women, both in developed and developing countries. At Dr. Soetomo Hospital, 77% of patients present at an advanced stage. Immuno-inflammatory cells play an important role in tumorigenesis and cancer progression. **Objective:** This study is an analytical study examining the role of the systemic immune-inflammation index (SII) as a prognostic factor in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy at Dr. Soetomo General Hospital, Surabaya. **Methods:** In this study, SII values were measured using data from complete blood count (CBC) and differential leukocyte count laboratory tests. SII values were obtained by calculating the NLR multiplied by the platelet count in units of 10^9 cells/L of blood fluid. **Results:** The SII values in this study sample varied within a range of 247 to 2306, with a mean value of 820.2 ± 448.3. Using a cut-off point of 900 to determine high or low SII groups, 36.1% of the samples had a high SII value (≥900), while the remaining 63.9% had a low SII value (<900). **Conclusion:** SII (Systemic Immune-Inflammation Index) has a significant relationship with the response to neoadjuvant chemotherapy in patients with locally advanced breast cancer. The use of SII as a predictive biomarker can assist in optimizing therapeutic strategies and patient monitoring.

Introduction

Breast cancer is the most prevalent malignancy and the leading cause of cancer-related deaths among women, both in developed and developing countries. According to the 2018 GLOBOCAN estimates by the International Agency for Research on Cancer (IARC), there were approximately 2.1 million new breast cancer cases worldwide (11.6% of all cancers), resulting in 626,679 deaths (15%).[1] In Indonesia, the prevalence of breast cancer is 0.5 per 1,000 women. Data from Dr. Soetomo Hospital indicates that 77% of patients present with advanced-stage disease. Over the past three years (2016-2018), the most common sites of metastasis among breast cancer patients at Dr. Soetomo General Hospital were bone (23%), lung (20%), and liver (12%).[2] Nevertheless, 20%-25% of patients diagnosed with locally advanced breast cancer experience higher rates of recurrence and mortality.

Immuno-inflammatory cells play a crucial role in tumorigenesis and cancer progression. Over time, studies have provided evidence that elevated inflammatory markers in peripheral blood also reflect the degree of

local inflammation within the tumor microenvironment. It's suggested that changes in the inflammatory characteristics of tumor cells can influence disease development and progression.[3,4] Other studies have also found that inflammatory responses hold potential as targets for targeted therapy or as indicators of prognosis in breast cancer.[5]

Inflammatory markers in the body are represented by neutrophils (N), lymphocytes (L), and platelets (P). Inflammation indicators such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have recently become hot topics due to their roles in the diagnosis, treatment, follow-up management, and prognostic prediction of various cancers, including gastric, lung, and breast cancers. These indicators are gaining popularity because they are considered non-invasive, easily accessible, and low-cost.

The use of the systemic immune-inflammation index (SII) as a predictive indicator in breast cancer remains controversial. Given the background described above, there is a need for further information regarding SII. Therefore, researchers are interested in investigating the relationship between the systemic immune-inflammation index (SII) and the assessment of neoadjuvant chemotherapy (NAC) response in breast cancer patients.

Method

This analytical study investigates the role of the systemic immune-inflammation index (SII) as a prognostic factor in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy at Dr. Soetomo General Hospital in Surabaya. The study employs a retrospective cohort design, utilizing secondary data obtained from medical records.

Patients were included if they had locally advanced breast cancer confirmed by biopsy, received neoadjuvant chemotherapy following diagnosis, and had complete blood laboratory and pathology results. Exclusion criteria encompassed male breast cancer patients, those with distant metastasis or inflammatory cancer, and individuals with co-morbid conditions such as autoimmune diseases, hematological disorders, or acute/chronic infectious diseases. Additionally, patients on anti-inflammatory or immunosuppressant medications and those who received blood product transfusions within one month prior to treatment were excluded.

Data collection will commence after securing official approval from Dr. Soetomo General Hospital, Surabaya. Once permission is granted, secondary data will be retrieved from the medical records of patients with locally advanced breast cancer who received neoadjuvant chemotherapy between 2022 and 2024. The collected data will include patient initials (to ensure confidentiality), general characteristics (gender, age, and nutritional status), disease stage, immunohistochemistry results, peripheral blood inflammatory marker results, and treatment outcomes. This information will then be meticulously recorded onto a dedicated data collection sheet.

Results

In this study, 72 samples met the inclusion criteria and were not subject to exclusion criteria. The sample characteristics were then described based on patient age, the type of neoadjuvant chemotherapy regimen received, breast cancer subtype, SII value, surgical status, pathology results according to the Miller Payne grading system, and radiological findings based on the RECIST classification.

Table 1. Characteristics of sample study

Variables	Frequency % (N)
Age (mean)	50,7 ± 10,2

<31 years	0 (0)
31 – 40 years	16,7 (12)
41 – 50 years	41,7 (30)
51 – 60 years	23,6 (17)
61 – 70 years	11,1 (8)
>70 years	6,9 (5)
NAC Regiments	
AC-T	9,7 (7)
CAF	66,7 (48)
FEC	0 (0)
TC	23,6 (17)
Breast Cancer Subtypes	
Her-2 type	2,8 (2)
Luminal B Her-2 Positive	22,2 (16)
Luminal B-Like Her-2 Negative	52,8 (38)
Luminal A	6,9 (5)
TNBC	15,3 (11)
Value of SII (mean)	820,2 ± 448,3
High (≥900)	36,1 (26)
Low (<900)	63,9 (46)
Operational Status	
Operable	69,4 (50)
Inoperable	30,6 (22)
Outcome Miller Payne	
Responsive	70,8 (51)
Unresponsive	29,2 (21)
RECIST Classification	

Complete Response	1,4 (1)
Partial Response	79,2 (57)
Progressive Disease	8,3 (6)
Stable Disease	11,1 (8)

Further analysis of the relationship between SII and patient surgical status using Risk Ratio (RR) revealed an RR of 0.513 (95% CI: 0.286 – 0.922). This clinically indicates that patients with a low SII value are potentially twice as likely to have a better neoadjuvant chemotherapy outcome compared to the high SII group.

Additionally, an analysis was conducted in this study regarding the association between the neoadjuvant chemotherapy regimen received by patients and their SII value. No significant correlation (p=0.287) was found between the neoadjuvant chemotherapy regimen administered and the patient's SII value.

Table 2. Correlation Analysis of SII with Subject Characteristics and Chemotherapy Response

Variable	SII Value		p-value	RR (95% CI)
	High n (%)	Low n (%)		
NAC Regiments				
AC-T	0 (0)	7 (100)	0.287	
CAF	19 (40)	29 (60)		
TC	7 (41)	10 (59)		
RECIST				
Complete Response	0 (0)	1 (100)		
Partial Response	22 (39)	35 (61)	0.025	
Progressive Disease	1 (17)	5 (83)		
Stable Disease	3 (38)	5 (62)		
Operational Status				
Operable	14 (28)	36 (72)	0.031	0.513 (0.286 – 0.922)
Inoperable	12 (56)	10 (44)		
Outcome Miller Payne				
Treatment Responsive	14 (27)	37 (73)	0.017	

Treatment Unresponsive	12 (57)	9 (43)	0.284 (0.098 – 0.820)

Discussions

The Systemic Immune-Inflammation Index (SII) is a widely recognized systemic inflammation indicator that has been extensively utilized as a prognostic biomarker across various cancer types, including breast cancer. This index is derived from simple hematological parameters: platelet count, neutrophil count, and lymphocyte count. Recent studies have demonstrated a correlation between elevated SII and poor prognosis in breast cancer patients, encompassing reduced overall survival and disease-free survival.[6] Inflammation plays a pivotal role in diverse aspects of tumor growth, angiogenesis, and metastasis, positioning SII as a significant predictor of treatment response and chemotherapy efficacy in patients.[7,8]

Neoadjuvant chemotherapy (NAC) is administered to reduce tumor size prior to surgical intervention in patients with locally advanced breast cancer. Current evaluation of NAC response employs various methodologies, notably the Miller-Payne Grading System and the Response Evaluation Criteria in Solid Tumors (RECIST). The Miller-Payne Grade assesses changes in tumor cell count between pre-chemotherapy biopsy and post-surgical tissue.[9] Conversely, RECIST categorizes response based on changes in tumor size using radiological imaging.[10-15] The combined application of these two methods offers a more comprehensive understanding of NAC effectiveness.

The findings of this study reveal a significant correlation between Miller-Payne outcomes and SII values in patients (p=0.017, RR: 0.284, 95% CI: 0.098 – 0.820). This correlation indicates that a lower patient SII is associated with a greater potential for responsiveness to NAC outcomes compared to those with higher SII values. This finding aligns with previous research suggesting that lower SII values are linked to a better histopathological response to chemotherapy.[7] A high SII reflects a more active inflammatory state and potential tumor immune tolerance, which can impede the effectiveness of neoadjuvant chemotherapy.[16] Beyond the Miller-Payne Grade, this study also identified a relationship between a lower SII and improved tumor response rates based on RECIST criteria (p=0.025). Patients with low SII were more prone to achieving a complete response (CR) or partial response (PR), in contrast to those with high SII. A meta-analysis similarly reported that a higher SII correlated with an increased risk of metastasis and resistance to neoadjuvant chemotherapy.[9] Consequently, SII can serve as an additional parameter for predicting NAC effectiveness based on radiological evaluation.

Furthermore, a low SII value before chemotherapy also correlated with an increased likelihood of patients becoming operable after neoadjuvant chemotherapy. This study found a significant correlation between SII values and patient surgical status (p=0.031; RR 0.513 95% CI: 0.286 – 0.922). This is consistent with a study which indicated that patients with a low SII have a better prognosis and higher survival rates following neoadjuvant chemotherapy.[16,17] A low SII reflects a more favorable balance between immune response and inflammation, which can enhance NAC effectiveness and enable more successful surgical interventions. These results suggest that patients with a lower systemic inflammatory status are more responsive to therapy, allowing them to undergo tumor resection surgery with higher success rates.[18,19] Conversely, patients with high SII more frequently experience significant residual tumors, hindering surgical efforts and increasing the risk of recurrence.[20,21]

Conclusion

There were no significant differences in the levels of fibroblast maturation, collagen deposition, or neovascularization between tracheas repaired with primary sutures and those repaired with fibrin glue.

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