

Association of HER-2 Status and Systemic Immune-Inflammation Index with Recurrence after Modified Radical Mastectomy for Breast Cancer: A Retrospective Cohort Study at Dr. Soetomo General Academic Hospital, Surabaya

Hendra Surya Atmaja^{1,2}, Desak Gede Agung Suprabawati^{1,2}, Dwi Hari Susilo^{1,2}

¹Department of Surgery, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

²Oncology Division, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

³Head and Neck Division, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

⁴Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

*Corresponding Author Email: hendrasuryaaa@gmail.com.

HOW TO CITE: ABSTRACT

Hendra Surya Atmaja, Desak Gede Agung Suprabawati, Dwi Hari Susilo (2026). Association of HER-2 Status and Systemic Immune-Inflammation Index with Recurrence after Modified Radical Mastectomy for Breast Cancer: A Retrospective Cohort Study at Dr. Soetomo General Academic Hospital, Surabaya International Journal of Special Education, 41(22s), 1290-1297

Recurrence after modified radical mastectomy (MRM) remains a major clinical problem in breast cancer, and simple, accessible prognostic markers are needed. Human epidermal growth factor receptor-2 (HER-2) status and the systemic immune-inflammation index (SII), calculated as platelet count $\times$ neutrophil count / lymphocyte count, have been proposed as prognostic markers, but evidence from Indonesian patients is scarce. This retrospective cohort study evaluated the association of HER-2 status and preoperative SII with recurrence in breast cancer patients who underwent MRM at Dr. Soetomo General Academic Hospital, Surabaya, between January 2018 and December 2023. Fifty-four patients with complete records were analysed (all women; mean age 53.35 ± 9.64 years; 64.8% with locally advanced disease; 51.9% HER-2 positive). Recurrence occurred in 14 patients (25.9%). Receiver operating characteristic (ROC) analysis showed poor discrimination of SII for recurrence (area under the curve [AUC] 0.587); the optimal cut-off of 362.29 gave a sensitivity of 85.71% but a specificity of only 37.5%. Recurrence occurred in 9 of 28 HER-2-positive patients (32.1%) and 5 of 26 HER-2-negative patients (19.2%) (Fisher's exact test, $p = 0.3582$), and in 12 of 37 patients with high SII (32.4%) and 2 of 17 with low SII (11.8%) ($p = 0.181$). In multivariable logistic regression, neither HER-2 positivity (odds ratio [OR] 1.92, 95% CI 0.54–7.41; $p = 0.319$) nor high SII (OR 3.51, 95% CI 0.80–24.79; $p = 0.133$) was an independent predictor of recurrence. HER-2 status and SII were not significantly associated with recurrence in this cohort. The large but imprecise odds ratio for

COPYRIGHT STATEMENT:

Copyright: © 2026 Authors.
Open access publication under the terms and conditions

of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>). high SII suggests a possible prognostic role that should be tested in larger prospective studies using time-to-event analysis.

Keywords: Breast cancer; HER-2; Systemic Immune-Inflammation Index; Recurrence; Modified Radical Mastectomy

Introduction

Breast cancer is the most common cancer among women worldwide. In 2022, an estimated 2.3 million women were diagnosed with breast cancer and 670,000 died of the disease.¹ Indonesia is among the countries with the highest numbers of breast cancer cases and deaths, ranking eighth for incidence and fourth for mortality in 2022.²

Breast cancer is treated with a multimodal approach that combines surgery with radiotherapy, chemotherapy, hormonal therapy and targeted therapy. Modified radical mastectomy (MRM), which removes the whole breast, including the skin, nipple and areola, together with most of the axillary lymph nodes while preserving the pectoral muscles, remains one of the principal operations.³ Despite good local control, recurrence continues to be a serious problem. The 10-year local recurrence rate after MRM has been reported at 12% to 27%,⁴ and recurrences can occur many years after the primary diagnosis.⁵

HER-2 is overexpressed in approximately 15% to 30% of invasive breast cancers and is associated with aggressive tumour behaviour and poorer clinical outcomes.⁶ Its status, assessed by immunohistochemistry (IHC), guides the use of HER-2-targeted agents such as trastuzumab, which have changed the prognosis of HER-2-positive disease.⁷ Systemic inflammation and host immunity also influence tumour progression. The systemic immune-inflammation index (SII) integrates peripheral platelet, neutrophil and lymphocyte counts ($SII = \text{platelets} \times \text{neutrophils} / \text{lymphocytes}$). Neutrophils and platelets are thought to promote tumour growth, angiogenesis and the survival of circulating tumour cells, whereas lymphocytes mediate antitumour immune surveillance, so that SII reflects the balance between host inflammatory and immune

status.⁸ SII can be calculated from a routine complete blood count, which makes it objective and inexpensive. A high SII has been associated with poor prognosis and recurrence in gastric cancer,⁹ colorectal cancer¹⁰ and breast cancer,^{8,11} including HER-2-positive disease.^{12,13}

However, the evidence remains inconsistent, and the relationship of HER-2 status and preoperative SII with recurrence after MRM has not been well described in Indonesian patients. This study therefore aimed to evaluate the predictive accuracy of SII and the association of HER-2 status and preoperative SII with recurrence in breast cancer patients who underwent MRM at Dr. Soetomo General Academic Hospital, Surabaya, between 2018 and 2023.

Methods

Study design and setting

This was an observational analytic retrospective cohort study conducted in the Department of Surgery, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Patients who underwent MRM between January 2018 and December 2023 were identified from medical records. The study was limited to a single institution to maintain uniform laboratory methods and the validity of the haematological data used to calculate SII. Ethical clearance was obtained from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital before data collection.

Participants

Patients diagnosed with breast cancer who underwent MRM in the Department of Surgery during the study period were included by consecutive sampling, provided that their HER-2 status (IHC) and preoperative complete blood count were documented. Patients diagnosed with early-stage or locally advanced breast cancer who

underwent modified radical mastectomy in the Department of Surgery, Dr. Soetomo General Academic Hospital, Surabaya, between January 2018 and December 2023 were included by consecutive sampling. Patients were excluded if their medical records were incomplete for the study variables or if the operation was performed outside Dr. Soetomo General Academic Hospital. The minimum sample size was calculated with the formula for correlative analytic studies (type I error 5%, type II error 20%, expected correlation coefficient 0.55), giving 25 patients per stage group (early stage and locally advanced) and a minimum total of 50 patients.

Data collection and variables

Data were extracted from electronic and paper medical records with a standardised data collection sheet, and patient identifiers were anonymised. Collected variables included age, sex, tumour location, clinical stage (early stage or locally advanced), comorbidities (hypertension, diabetes mellitus, previous stroke, chronic gastritis and autoimmune disease), and adjuvant treatment. HER-2 status was taken from the IHC result in the pathology report and classified as positive or negative. SII was calculated from the last preoperative complete blood count as $(\text{platelet count} \times \text{neutrophil count}) / \text{lymphocyte count}$. The outcome was recurrence, defined as locoregional or distant metastatic recurrence documented in the follow-up medical records during the observation period.

Statistical analysis

Data were analysed with the Statistical Package for the Social Sciences (SPSS) version 23.0. Continuous variables are presented as mean $\pm$ standard deviation and categorical variables as

numbers and percentages. The discriminative ability of SII for recurrence was assessed with a receiver operating characteristic (ROC) curve and the area under the curve (AUC). The optimal cut-off value was determined with the Youden index, and sensitivity and specificity were calculated at this cut-off. Patients were then classified into high-SII and low-SII groups. The associations of HER-2 status and SII category with recurrence were tested with the chi-square test, or Fisher's exact test when the assumptions were not met, and the strength of correlation was evaluated with Spearman's rank correlation. Binary logistic regression including HER-2 status and SII was used to estimate odds ratios (OR) with 95% confidence intervals (CI). Models with SII as a categorical variable and as a continuous variable were compared with the Akaike information criterion (AIC), where a lower value indicates a better fit. A two-sided p-value below 0.05 was considered statistically significant.

Results

Characteristics of the study population

During 2018–2023, 459 breast cancer patients were recorded at Dr. Soetomo General Academic Hospital, of whom 230 presented with locally advanced breast cancer and 87 were HER-2 positive. Of the 459 patients, 405 had incomplete records because of the transition from the old to the new electronic medical record system, leaving 54 patients for analysis. The characteristics of these patients are shown in Table 1. All patients were women, with a mean age of 53.35 ± 9.64 years. Nearly two-thirds of the patients (64.8%) had locally advanced disease, and 28 patients (51.9%) were HER-2 positive. Recurrence occurred in 14 patients (25.9%).

Table 1. Baseline characteristics of breast cancer patients who underwent modified radical mastectomy (n = 54)

Characteristic	Value
Age, years, mean $\pm$ SD	53.35 ± 9.64
Sex, n (%)	

Characteristic	Value
Female	54 (100)
Male	0 (0)
Clinical stage, n (%)	
Early stage	19 (35.2)
Locally advanced	35 (64.8)
HER-2 status, n (%)	
Positive	28 (51.9)
Negative	26 (48.1)
Tumour location, n (%)	
Left breast	28 (51.9)
Right breast	26 (48.1)
Comorbidity, n (%)	
Absent	34 (63.0)
Present	20 (37.0)
SII, mean $\pm$ SD	589.26 $\pm$ 351.52
SII category, n (%)	
High (>362.29)	37 (68.5)
Low (≤ 362.29)	17 (31.5)
Recurrence, n (%)	
Yes	14 (25.9)
No	40 (74.1)

SD, standard deviation; SII, systemic immune-inflammation index (platelets $\times$ neutrophils / lymphocytes); HER-2, human epidermal growth factor receptor-2.

Predictive accuracy of SII for recurrence

The ROC curve of SII for predicting recurrence is shown in Figure 1. The AUC was 0.587,

indicating poor discrimination between patients with and without recurrence. The optimal cut-off determined with the Youden index was 362.29. At this cut-off, SII had a sensitivity of 85.71% but a specificity of only

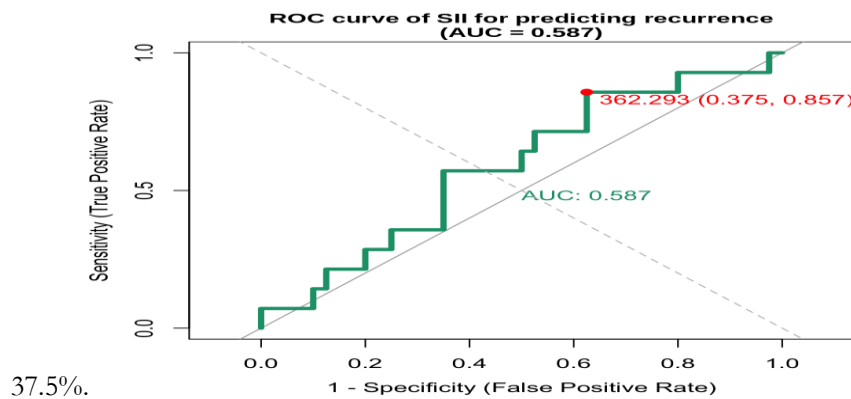


Figure 1. Receiver operating characteristic (ROC) curve of SII for predicting recurrence. The red dot marks the optimal cut-off (362.29; specificity 0.375, sensitivity 0.857).

Association of HER-2 status and SII with recurrence

The results of the bivariate analyses are shown in Table 2. Recurrence occurred in 9 of 28 HER-2-positive patients (32.1%) and in 5 of 26 HER-2-negative patients (19.2%). This difference was not statistically significant (Fisher's exact test, $p = 0.3582$), and Spearman's correlation showed a very weak, non-significant positive correlation between HER-2 status and recurrence ($\rho = 0.1472$, $p = 0.2881$).

Recurrence was more frequent in the high-SII group (12 of 37 patients, 32.4%) than in the low-SII group (2 of 17 patients, 11.8%), with an estimated odds ratio of 3.526. However, the difference was not statistically significant (Fisher's exact test, $p = 0.181$). Spearman's correlation between continuous SII and recurrence was likewise very weak and not significant ($\rho = 0.1328$, $p = 0.3382$).

Table 2. Association of HER-2 status and SII category with recurrence

Variable	Recurrence, n (%)	No recurrence, n (%)	Total, n	Fisher's exact p	Spearman's rho (p)
HER-2 status				0.3582	0.1472 (0.2881)
Positive	9 (32.1)	19 (67.9)	28		
Negative	5 (19.2)	21 (80.8)	26		
SII category				0.181	0.1328 (0.3382)*
High (>362.29)	12 (32.4)	25 (67.6)	37		
Low ($\leq$ 362.29)	2 (11.8)	15 (88.2)	17		

SII, systemic immune-inflammation index. Percentages are row percentages. *Spearman's correlation was calculated for continuous SII values.

Multivariable logistic regression

The model with SII as a categorical variable (cut-off 362.29) had a lower AIC (63.923) than the model with continuous SII (65.733) and was therefore used (Table 3). High SII was associated

with an odds ratio of 3.51 (95% CI 0.80–24.79; $p = 0.133$) for recurrence, and HER-2 positivity with an odds ratio of 1.92 (95% CI 0.54–7.41; $p = 0.319$). Neither variable was a statistically

significant independent predictor of recurrence. The wide confidence interval for high SII indicates that the estimate is imprecise.

Table 3. Multivariable binary logistic regression for recurrence (n = 54, 14 events)

Variable	Odds ratio	95% CI	p-value
HER-2 positive (vs negative)	1.92	0.54–7.41	0.319
High SII, >362.29 (vs ≤ 362.29)	3.51	0.80–24.79	0.133

CI, confidence interval; SII, systemic immune-inflammation index.

Discussion

In this retrospective cohort of 54 women who underwent MRM at a tertiary referral hospital, SII showed poor discrimination for recurrence (AUC 0.587), and neither HER-2 status nor SII category was significantly associated with recurrence. Patients with high SII had a numerically higher odds of recurrence (OR 3.51), but the confidence interval (0.80–24.79) was very wide, so the study can neither confirm nor exclude a prognostic role of SII.

Most patients (64.8%) presented with locally advanced disease. Across the institution, 230 of the 459 recorded breast cancer patients (50.1%) had locally advanced breast cancer, which probably reflects the role of Dr. Soetomo General Academic Hospital as a tertiary referral centre. HER-2 positivity in the institutional series (87 of 459 patients, 19.0%) lies within the 15% to 30% range reported in the literature.⁶

The optimal SII cut-off in our cohort (362.29) gave a high sensitivity (85.71%) but a low specificity (37.5%). A test with this profile misses few recurrences but classifies many patients who do not recur as high risk. In our data, 25 of the 37 patients in the high-SII group did not develop recurrence. The low specificity may be partly explained by the fact that SII is a dynamic marker that is influenced by infection, corticosteroid use and the physiological stress response,¹⁴ and it was measured only once before surgery. The cut-off also differed from the value of 514 reported in 784 patients with resected breast cancer, in which SII was a prognostic factor for disease-free and overall survival and was correlated with HER-2

status.⁸ Studies in HER-2-positive disease have also reported that SII was associated with prognosis and the efficacy of neoadjuvant chemotherapy,¹² whereas in another cohort SII had no prognostic value among HER-2-positive patients who did not receive trastuzumab.¹³ Cut-off values therefore appear to depend on the population and dataset, and the published findings on SII in breast cancer remain controversial.¹¹

Recurrence was numerically more frequent in HER-2-positive patients (32.1%) than in HER-2-negative patients (19.2%), which is consistent with the aggressive biology of HER-2-positive tumours,⁶ but the difference was not significant ($p = 0.3582$). Some HER-2-positive patients may have received HER-2-targeted therapy, which lowers the risk of recurrence⁷ and may have attenuated the difference. However, treatment was not compared in this study, and no conclusion about the effectiveness of any therapy can be drawn. In addition, hormone receptor status and molecular subtype were not analysed, so the HER-2-negative group may be heterogeneous and may include aggressive subtypes such as triple-negative disease.

In the multivariable model, neither HER-2 positivity nor high SII was an independent predictor of recurrence. An odds ratio of 3.5 is clinically substantial, and even without statistical significance it may justify closer postoperative surveillance of patients with a high SII. However, with only 14 recurrences the estimate is unstable, as shown by the confidence interval, and the result should be interpreted as a trend that needs

confirmation. Clinically, SII and HER-2 status alone are not sufficient as single predictors of recurrence after MRM in this setting, and clinicians should not rely on a single laboratory parameter to determine prognosis. Future studies should collect blood samples at a standardised time immediately before surgery to avoid bias from the acute stress response.¹⁴

This study has several limitations. First, its retrospective design and the transition of the electronic medical record system resulted in incomplete records for 405 of 459 patients, so only 54 patients were analysed. This reduced statistical power and may have introduced selection bias. Second, details of chemotherapy regimens, radiotherapy and the duration of hormonal therapy could not be entered into the model, so residual confounding is possible. Third, follow-up duration varied between patients, although recurrence is time-dependent and may occur many years after treatment;⁵ logistic regression does not account for time to recurrence, and time-to-event methods such as Cox proportional hazards regression would be more appropriate in future studies. Fourth, the SII cut-off was derived from the same dataset in which it was tested and needs external validation. Finally, this was a single-centre study, and the findings may not be generalisable to other populations. Larger, multicentre prospective studies with longer and more uniform follow-up are needed to validate the prognostic role of SII and HER-2 status.

Conclusion

SII showed poor discrimination for recurrence after MRM in this cohort (AUC 0.587). At the optimal cut-off of 362.29, the sensitivity was 85.71% and the specificity 37.5%. Neither HER-2 status ($p = 0.3582$) nor SII ($p = 0.181$) was significantly associated with recurrence, and neither was an independent predictor in multivariable analysis. The trend towards a higher odds of recurrence in patients with high SII (OR 3.51, 95% CI 0.80–24.79) suggests that SII may

still have value as a prognostic marker, but this needs confirmation in larger prospective studies with more recurrence events, complete adjustment for adjuvant therapy and time-to-event analysis.

Acknowledgements

The authors would like to thank the medical records staff and clinical staff of Dr. Soetomo General Academic Hospital, Surabaya, for their assistance with data collection.

Declarations

Ethics approval and consent to participate:

This study was approved by the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya.

Consent for publication: Not applicable. No identifiable individual patient data are presented.

Availability of data and material: The data supporting the findings of this study are summarised in this article. The anonymised dataset is available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: None.

Authors' contributions: HSA designed the study, collected and analysed the data, and wrote the manuscript. DGAS and DHS supervised the study and revised the manuscript for intellectual content. All authors read and approved the final manuscript.

Authors' information: HSA is a resident in Surgery at the Department of Surgery, Faculty of Medicine, Universitas Airlangga, and Dr. Soetomo General Academic Hospital. DGAS is a consultant surgical oncologist and DHS is a consultant in head and neck surgical oncology; both are staff members of the Department of Surgery, Faculty of Medicine, Universitas Airlangga.

References

- World Health Organization. Breast cancer [Internet]. Geneva: World Health Organization; 2025 [cited 2026 Sep 21]. Available from: <https://www.who.int/news-room/fact-sheets/detail/breast-cancer>
- Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, et al. Global Cancer Observatory: Cancer Today [Internet]. Lyon: International Agency for Research on Cancer; 2024 [cited 2026 Sep 21]. Available from: <https://gco.iarc.who.int/today>
- Bland KI, Copeland EM, Klimberg VS, Gradishar WJ, editors. The breast: comprehensive management of benign and malignant diseases. 5th ed. Philadelphia: Elsevier; 2018.
- Kheradmand AA, Ranjbarnovin N, Khazaeipour Z. Postmastectomy locoregional recurrence and recurrence-free survival in breast cancer patients. *World J Surg Oncol*. 2010;8:30. doi:10.1186/1477-7819-8-30
- Pedersen RN, Esen BÖ, Mellekjær L, et al. The incidence of breast cancer recurrence 10-32 years after primary diagnosis. *J Natl Cancer Inst*. 2022;114(3):391–9.
- Iqbal N, Iqbal N. Human epidermal growth factor receptor 2 (HER2) in cancers: overexpression and therapeutic implications. *Mol Biol Int*. 2014;2014:852748. doi:10.1155/2014/852748
- Mitri Z, Constantine T, O'Regan R. The HER2 receptor in breast cancer: pathophysiology, clinical use, and new advances in therapy. *Chemother Res Pract*. 2012;2012:743193. doi:10.1155/2012/743193
- Li W, Ma G, Deng Y, Chen W, Liu Z, Chen F, et al. Systemic immune-inflammation index is a prognostic factor for breast cancer patients after curative resection. *Front Oncol*. 2021;11:570208. doi:10.3389/fonc.2021.570208
- Wang Q, Zhu D. The prognostic value of systemic immune-inflammation index (SII) in patients after radical operation for carcinoma of stomach in gastric cancer. *J Gastrointest Oncol*. 2019;10(5):965–78. doi:10.21037/jgo.2019.05.03
- Yatabe S, Eto K, Haruki K, et al. Signification of systemic immune-inflammation index for prediction of prognosis after resecting in patients with colorectal cancer. *Int J Colorectal Dis*. 2020;35(8):1549–55. doi:10.1007/s00384-020-03615-w
- Zhou Y, Guo X, Shen L, Liu K, Sun Q, Wang Y, et al. Predictive significance of systemic immune-inflammation index in patients with breast cancer: a retrospective cohort study. *Onco Targets Ther*. 2023;16:939–60. doi:10.2147/OTT.S434193
- Gu Q, Zhao J, Liu Y, Chen H, Wang L. Association between the systemic immune-inflammation index and the efficacy of neoadjuvant chemotherapy, prognosis in HER2 positive breast cancer—a retrospective cohort study. *Gland Surg*. 2023;12(5):609–18. doi:10.21037/gs-23-55
- Pang J, Ding N, Yin N, Xiao Z. Systemic immune-inflammation index as a prognostic marker in HER2-positive breast cancer patients undergoing trastuzumab therapy. *Sci Rep*. 2024;14(1). doi:10.1038/s41598-024-57343-0
- Shevchenko I, et al. The value of systemic inflammatory indices for predicting early postoperative complications in colorectal cancer. *Medicina (Kaunas)*. 2024;60(9). doi:10.3390/medicina60091481