

Systemic inflammation response index as a predictor of distant metastasis in breast cancer patients

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Abstract

Introduction: The Systemic Inflammation Response Index (SIRI) reflects systemic inflammation and immune response. Elevated SIRI has been linked to poor cancer outcomes by promoting tumor progression and metastasis. This study evaluates the relationship between pre-treatment SIRI and distant metastasis in breast cancer patients.

Methods: This retrospective cross-sectional study analyzed medical records of breast cancer patients at Margono Soekarjo Country Hospital between 2022 and 2024, with 869 patients included for analysis. Pre-treatment SIRI was calculated from complete blood count parameters. Metastatic status was confirmed by imaging and/or histopathology. SIRI was defined as neutrophils and monocytes divided by lymphocytes. Statistical analyses included comparison of SIRI between metastatic and non-metastatic groups, ROC analysis, and multivariable logistic regression to evaluate the discriminative ability and independent association of SIRI with distant metastasis, adjusting for age, histopathological type, and molecular subtype.

Results: Pre-treatment SIRI was significantly higher in the metastatic group than in the non-metastatic group (mean $\pm$ SD: 2.49 ± 2.68 vs. 0.41 ± 0.49 ; $p < 0.001$). ROC analysis identified an optimal SIRI cut-off of >0.60 , yielding 86% sensitivity, 85% specificity, and an AUC of 0.90, indicating excellent discriminatory performance. In multivariable logistic regression, higher SIRI independently predicted distant metastasis after adjustment of the confounding factors, with each one-unit increase associated with substantially increased odds (adjusted OR = 12.28; 95% CI: 8.22–18.33; $p < 0.001$).

Conclusion: Pre-treatment SIRI showed an association with distant metastasis in breast cancer, indicating its potential as a low-cost and non-invasive prognostic biomarker.

Keywords: Breast cancer, Distant Metastasis, Prognostic Biomarker, Systemic Inflammation Response Index (SIRI)

Abstrak

Pendahuluan: Systemic Inflammation Response Index (SIRI) mencerminkan inflamasi sistemik dan respons imun. Peningkatan SIRI telah dikaitkan dengan luaran kanker yang buruk melalui perannya dalam mendorong progresi tumor dan metastasis. Penelitian ini mengevaluasi hubungan antara SIRI sebelum terapi dan metastasis jauh pada pasien kanker payudara.

Metode: Penelitian potong lintang retrospektif ini menganalisis rekam medis pasien kanker payudara di RSUD Prof. Dr. Margono Soekarjo pada periode 2022–2024, dengan total 869 pasien yang diikutsertakan dalam analisis. SIRI sebelum terapi dihitung berdasarkan parameter pemeriksaan darah lengkap. Status metastasis dikonfirmasi melalui pemeriksaan pencitraan dan/atau histopatologi. SIRI didefinisikan sebagai jumlah neutrofil dikalikan monosit, kemudian dibagi limfosit. Analisis statistik meliputi perbandingan nilai SIRI antara kelompok metastasis dan nonmetastasis, analisis ROC, serta regresi logistik multivariat untuk mengevaluasi kemampuan diskriminatif dan hubungan independen SIRI dengan metastasis jauh, dengan penyesuaian terhadap usia, tipe histopatologi, dan subtype molekuler.

Hasil: Nilai SIRI sebelum terapi secara signifikan lebih tinggi pada kelompok metastasis dibandingkan kelompok nonmetastasis (rerata $\pm$ SD: $2,49 \pm 2,68$ vs. $0,41 \pm 0,49$; $p < 0,001$). Analisis ROC mengidentifikasi nilai cut-off SIRI optimal $>0,60$, dengan sensitivitas 86%, spesifisitas 85%, dan AUC 0,90, yang menunjukkan kemampuan diskriminatif yang sangat baik. Pada regresi logistik multivariat, SIRI yang lebih tinggi secara independen memprediksi metastasis jauh setelah dilakukan penyesuaian terhadap faktor-faktor perancu, dengan setiap peningkatan satu unit SIRI berhubungan dengan peningkatan odds yang substansial (adjusted OR = 12,28; 95% CI: 8,22–18,33; $p < 0,001$).

Kesimpulan: SIRI sebelum terapi menunjukkan hubungan dengan metastasis jauh pada kanker payudara, yang mengindikasikan potensinya sebagai biomarker prognostik yang murah dan noninvasif.

Kata kunci: Kanker payudara, metastasis jauh, biomarker prognostik, Systemic Inflammation Response Index (SIRI)

Background

Breast cancer is the most frequently diagnosed cancer among women worldwide, accounting for more than 10% of all newly diagnosed cancer cases annually. It is also the second leading cause of cancer-related morbidity and mortality.¹ According to the GLOBOCAN 2020 database, approximately 2,261,419 new cases of breast cancer and 684,996 breast cancer-related deaths were reported globally.² Breast cancer is a biologically heterogeneous disease that can be classified into four major molecular subtypes based on hormone receptor and human epidermal growth factor receptor 2 (HER2) status, namely luminal A, luminal B, HER2-overexpressing, and triple-negative breast cancer, each associated with distinct clinical behaviors and prognostic outcomes.³ Despite advances in diagnosis and treatment, distant metastasis remains the principal cause of breast cancer-related mortality, underscoring the need for reliable biomarkers to identify patients at high risk of metastatic progression.

Chronic inflammation has been increasingly recognized as a critical driver of cancer progression, contributing to tumor proliferation, invasion, immune evasion, and metastatic dissemination. Inflammation-based biomarkers derived from peripheral blood parameters have gained attention due to their accessibility and potential clinical utility. Recent studies have demonstrated that the systemic inflammation response index (SIRI), a blood-based inflammatory biomarker, has significant prognostic value in predicting clinical outcomes in various solid tumors.³ Since its introduction as a prognostic marker in pancreatic cancer in 2016, SIRI has demonstrated prognostic value across various solid malignancies.⁴ In breast cancer, however, existing studies evaluating SIRI have produced inconsistent results. Some studies have reported that elevated SIRI is significantly associated with poorer overall and disease-free survival. Wang et al. (2020) reported that breast cancer patients with a SIRI ≤ 0.65 had significantly better overall survival than those with a SIRI > 0.65 ($P < 0.001$).⁵ Similarly, Zhu et al. (2022) found that patients with low SIRI had longer disease-free survival (41.50 vs. 37.63 months) and overall survival (64.57 vs. 58.42 months) compared with those with high SIRI.⁶ The others have failed to demonstrate a significant prognostic. These discrepancies may be explained by heterogeneity in study populations, molecular subtypes, disease stages, treatment strategies, SIRI cut-off values, and selected clinical endpoints. Importantly, most previous investigations have focused primarily

on survival outcomes, whereas the predictive role of SIRI for distant metastasis remains insufficiently explored. To the best of our knowledge, this study is among the first to specifically evaluate the systemic inflammation response index as a predictor of distant metastasis in breast cancer patients. By focusing on metastatic outcomes rather than survival alone, this study aims to address an important gap in the literature and to clarify the clinical utility of SIRI as a simple and reliable biomarker for metastatic risk stratification.

Methods

This retrospective cross-sectional study was conducted using medical record data from breast cancer patients treated at Margono Soekarjo County Hospital between January 2022 and December 2024. A total of 4,432 breast cancer patients were identified; 869 were eligible, including 520 patients with distant metastasis and 349 patients with non-distant metastasis. Eligible patients had a histopathological confirmation and immunohistochemical examination of breast cancer, available complete blood count (CBC) data obtained prior to any treatment, and documented evaluation of metastasis. The presence of distant metastasis was confirmed through imaging modalities and/or histopathological examination. Patients with incomplete clinical data or missing pre-treatment laboratory results were excluded.

The systemic inflammation response index (SIRI) was calculated for each patient using pre-treatment CBC parameters. SIRI was defined as the product of neutrophil and monocyte counts divided by the lymphocyte count (neutrophils $\times$ monocytes / lymphocytes). All hematological parameters were obtained from routine laboratory examinations performed at the time of diagnosis, prior to the initiation of systemic or local cancer therapy.

Patients were categorized into metastatic and non-metastatic groups based on the presence of distant metastasis at diagnosis. Comparative analyses were performed to evaluate differences in SIRI values between the two groups. Receiver operating characteristic (ROC) curve analysis was used to assess the discriminative ability of SIRI in predicting distant metastasis and to determine the optimal cut-off value, based on the highest Youden index.

To identify whether SIRI was independently associated with distant metastasis, multivariable logistic regression analysis was conducted. Potential confounding variables included in the model were age, tumor

stage, and breast cancer receptor subtype. Results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using appropriate statistical software.

Results

Patients were categorized into metastatic and non-metastatic groups. The baseline characteristics of the study population are summarized in Table 1. Age did not differ significantly between the distant and non-distant metastasis groups (51 ± 11 vs. 52 ± 10 years; $p = 0.063$). Histopathological type showed a significant difference in distribution between groups ($p < 0.001$), with invasive ductal cancer being the most common histology in both groups (70% vs. 68%), followed by invasive lobular cancer, mixed histology, NST, and other types in smaller proportions. Molecular subtype distribution also differed significantly ($p < 0.001$); luminal A was the predominant subtype in the non-distant metastasis group (52% vs. 18%), whereas luminal B, HER2-positive, and triple-negative subtypes accounted for a larger proportion of cases in the distant metastasis group. Median pre-treatment SIRI was significantly higher in patients with distant metastasis than in those without (1.72 [IQR 2.04] vs. 0.27 [IQR 0.28]; $p < 0.001$).

Table 1. Characteristics of patients

Variable	Distant Metas n (%)	Non-Distant n (%)	p-value
Number of patients	520	349	
Age (mean $\pm$ SD)	51 ± 11	52 ± 10	
Age Group			0.063
<40 years	77(15)	33(9)	
40–50 years	171(33)	118(34)	
>50 years	272(52)	198(57)	
Histopathology type			<0.001
IDC	363(70)	239(68)	
ILC	56(11)	58(17)	
Mixed	28(5)	31(9)	
NST	53(10)	15(4)	
Others	20(4)	6(2)	
Molecular subtype			<0.001
Luminal A	93(18)	182(52)	
Luminal B	173(33)	95(27)	
HER2 Positive	105(20)	45(13)	
Triple Negative	149(29)	27(8)	
SIRI (Median, IQR)	1.72, 2.04	0.27, 0.28	<0.001

IDC : Invasive Ductal Carcinoma, ILC : Invasive Lobular Carcinoma, Mixed : IDC + ILC, NST : No Special Type, Others : tubular, medular, mucinous, cribriform, papillary, micropapillary, and Paget disease. (%) : percentage within each group

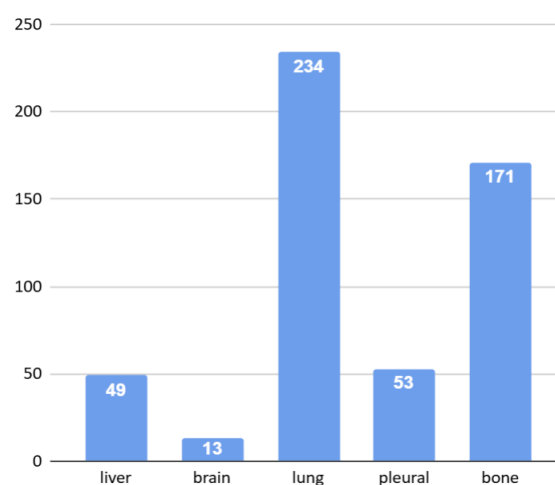


Figure 1. Distant metastasis distribution

The distribution of distant metastatic sites among breast cancer patients is illustrated in Figure 1. The lung was the most common site of distant metastasis, observed in 234 patients, followed by bone metastasis in 171 patients. Pleural involvement was identified in 53 patients, while liver metastasis was present in 49 patients. Brain metastasis was the least frequent, occurring in 13 patients. Overall, pulmonary and skeletal sites accounted for the majority of distant metastatic involvement in this study.

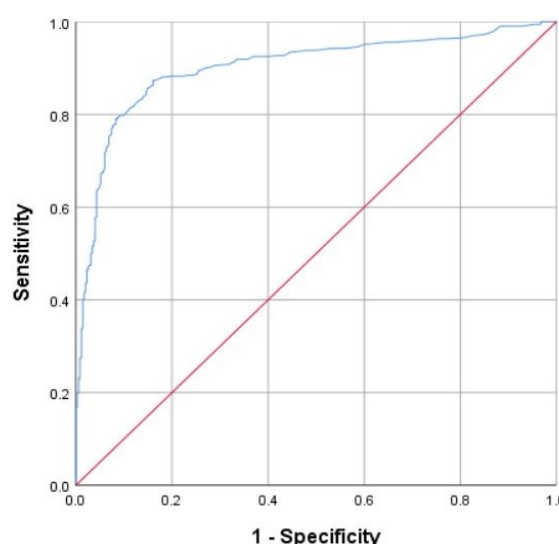


Figure 2. ROC Curve

Receiver operating characteristic (ROC) curve analysis demonstrated that the systemic inflammation response index (SIRI) had strong discriminatory ability for predicting the presence of distant metastasis in breast cancer patients. The optimal cut-off value was identified as $\text{SIRI} > 0.60$, which yielded a sensitivity of 86% and a specificity of 85%. The area under the ROC curve (AUC) was 0.90 (Figure 2), indicating very good diagnostic performance and clinically relevant discrimination between metastatic and non-metastatic disease.

Pre-treatment SIRI values were significantly higher in patients with distant metastasis compared with those without metastasis ($p < 0.001$). The distant metastatic group had a mean SIRI of 2.49 (SD = 2.68), whereas the non-distant metastatic group had a lower mean SIRI of 0.41 (SD = 0.49), indicating a markedly increased systemic inflammatory response among patients with metastatic disease.

Multivariable logistic regression analysis demonstrated that higher SIRI levels were independently associated with an increased likelihood of distant metastasis after adjustment for age, histological type, and molecular subtype. SIRI was analyzed as a continuous variable in the multivariable model. Each one-unit increase in SIRI was associated with a more than twelve-fold increase in the odds of distant metastasis (adjusted OR = 12.28; 95% CI: 8.22–18.33; $p < 0.001$). Age was inversely associated with distant metastasis (adjusted OR = 0.71; 95% CI: 0.54–0.93; $p = 0.014$), while histological type (adjusted OR = 1.23; 95% CI: 1.03–1.48; $p = 0.023$) and molecular subtype (adjusted OR = 2.01; 95% CI: 1.66–2.42; $p < 0.001$) were also identified as independent predictors of distant metastasis. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminatory performance of SIRI. However, ROC-derived SIRI cut-off values were used for exploratory purposes only and were not applied to define categorical variables in the primary multivariable analysis.

Discussion

The systemic inflammation response index (SIRI), which integrates neutrophil and monocyte counts relative to lymphocytes, reflects the balance between tumor-promoting inflammation and anti-tumor immune surveillance. In the present study, an elevated SIRI was associated with adverse clinic-pathological features and poorer outcomes, supporting its role as a prognostic biomarker. Our findings

highlight the relevance of systemic inflammation in the metastatic process of breast cancer. Based on the distribution illustrated in Figure 1, metastatic involvement was grouped into lung, pleural, liver, brain, and bone sites. Patients with distant metastasis exhibited significantly higher SIRI values compared with non-metastatic patients (median 1.72 vs 0.27, $p < 0.001$), suggesting that a heightened inflammatory state may facilitate tumor dissemination. High SIRI indicates pro-tumorigenic inflammation, in which neutrophils promote invasion and metastasis while monocytes differentiate into tumor-associated macrophages (TAMs) that foster progression; lymphocytes provide anti-tumor immunity. Neutrophils promote invasion, angiogenesis, and metastatic niche formation, while circulating monocytes can differentiate into TAMs that support tumor progression and immune evasion. Conversely, lymphocytes play a central role in antitumor immunity, and reduced lymphocyte counts reflect impaired immune surveillance. Together, these mechanisms provide a biological rationale for the observed association between elevated SIRI and distant metastasis.⁷

Our study reported that SIRI and distant metastases were related with the p -value of < 0.001 . Further multivariable analysis was performed to adjust for potential confounders. Higher SIRI was independently associated with a more than twelve-fold increase in the odds of distant metastasis for each one-unit increase in SIRI (adjusted OR 12.28; 95% CI 8.22–18.33; $p < 0.001$). As shown in Figure 2, the ROC curve demonstrates strong discriminative performance. The sensitivity reached 86% and the specificity 85%. The area under the ROC curve (AUC) was 0.90, indicating that the model has good-to-excellent accuracy in distinguishing between outcome groups.

Previous studies have explored the prognostic value of SIRI in breast cancer, particularly in relation to treatment response and survival outcomes. Pre-treatment SIRI was a more crucial and integral prognostic index for patients with breast malignant tumors receiving neoadjuvant chemotherapy (NACT).⁸ It may assist clinicians in predicting patient prognosis and in evaluating treatment response. In this context, a SIRI threshold of 0.72 demonstrated significant predictive value for response to NACT, particularly in relation to pathological complete response (pCR).^{8,9} Conversely, higher SIRI levels were associated with poorer survival outcomes as well as more advanced tumor and nodal stages. In a

2025 study of 348 breast cancer patients (185 non-metastatic, 163 distant metastatic), Boruta and LASSO analyses identified SIRI as one of five key biomarkers (with ALI, MLR, AGR, GNRI) for distant metastasis risk. Elevated SIRI independently increased metastasis odds (OR 1.38 per standardized unit, 95% CI: 1.05–1.81), with median SIRI higher in metastatic cases (0.98 vs. 0.80). ROC analysis showed moderate predictive accuracy (AUC 0.608, cutoff 0.974). These findings are consistent with previous studies in breast cancer cohorts, which have reported SIRI cutoff values ranging from 0.65 to 0.80, further underscoring the relevance of SIRI as an inflammation-based prognostic indicator.¹⁰

The median age of the patients was 52 years. Participants were stratified by age into reproductive stage: <40 years (predominantly reproductive age), 40–50 years (perimenopausal transition), and >50 years (predominantly postmenopausal). The relationship between age and SIRI may be influenced by multiple sources of bias, including comorbid conditions, chronic low-grade inflammation associated with aging, hormonal status, and non-cancer-related inflammatory processes. Importantly, to date, no studies have reported a strong, direct positive or negative correlation between SIRI and age specifically within distant metastatic breast cancer populations, highlighting a relevant research gap and underscoring the need for further focused investigation.³ This study reported that histological type emerged as an independent predictor of distant metastasis after multivariable adjustment (adjusted OR = 1.23; 95% CI 1.03–1.48; $p = 0.023$). Although the magnitude of association was modest compared with SIRI and molecular subtype, this finding suggests that tumor histology contributes independently to metastatic potential. No study related to SIRI and histopathological subtype. Variations in tumor architecture, stromal interaction, and patterns of local invasion across histological subtypes may underlie these differences in metastatic behavior.

Invasive ductal carcinoma (IDC) constituted the majority of cases, consistent with prior epidemiological reports, while invasive lobular carcinoma (ILC) and mixed histologies accounted for smaller proportions. Previous studies have shown that ILC, despite often presenting with favorable receptor profiles, may exhibit distinct metastatic patterns and delayed dissemination, which could partially explain its independent association with distant metastasis. The relatively weaker effect size observed in this study suggests that histological type is a contributory

factor rather than a dominant determinant of metastatic risk, particularly when systemic inflammatory burden and molecular characteristics are taken into account.¹¹

Molecular subtype demonstrated a strong and statistically significant association with distant metastasis (adjusted OR = 2.01; 95% CI 1.66–2.42; $p < 0.001$), underscoring its central role in breast cancer progression. This finding aligns with established evidence that intrinsic tumor biology, reflected by hormone receptor and HER2 status, critically influences metastatic behavior and clinical outcomes. Previous findings showed that patients with ER/PR-negative status had a higher proportion of high SIRI (25.0% and 23.0%, respectively) compared with those with ER/PR-positive status (11.6% and 10.4%; $P = 0.005$ and $P = 0.006$, respectively).¹² As in this study, the analyses were performed based on molecular subtypes rather than individual biomarkers (ER, PR, HER2, and Ki-67), because molecular subtyping represents an integrated biological classification that reflects tumor hormone dependency, proliferative activity, and oncogenic signaling pathways.

More aggressive subtypes, particularly HER2-positive and triple-negative breast cancers, are known to exhibit higher proliferative activity, genomic instability, and early metastatic spread, which is consistent with the elevated odds observed in this study. In contrast, luminal subtypes, especially luminal A, generally demonstrate more indolent disease courses and lower metastatic potential. The robust independent effect of molecular subtype in our multivariable model highlights that biological aggressiveness remains a key driver of distant metastasis, even after adjusting for histology and systemic inflammatory markers such as SIRI.^{11, 13, 14}

Meta-analyses show elevated SIRI links to larger tumors (T3-T4 OR=1.73), advanced stages, and poor OS across breast cancer, with subtype-specific prognostic roles (e.g., stronger in HER2+).³ Direct SIRI-histopathological type correlations remain unreported in metastatic breast cancer, focusing instead on prognostic independence. Increased neutrophil and monocyte counts may promote tumor progression by secreting pro-inflammatory cytokines, angiogenic factors, and immunosuppressive mediators, while reduced lymphocyte levels reflect impaired antitumor immunity. This inflammatory milieu may contribute to chemotherapy resistance and aggressive tumor behavior, explaining the observed association between high SIRI and unfavorable treatment

response and prognosis. As SIRI is derived from routine complete blood count parameters, it represents a low-cost, readily available, and non-invasive biomarker that can be easily implemented in daily clinical practice. Elevated SIRI at diagnosis may help identify patients who require more intensive metastatic workup, closer surveillance, or earlier systemic treatment strategies, particularly in resource-limited settings.

Nevertheless, several limitations should be acknowledged. The retrospective nature of the study precludes definitive conclusions regarding causality. Differences in study populations, endpoints, and analytical methods across existing studies limit direct generalizability and highlight the need for standardized cutoff calibration. Furthermore, non-cancer-related inflammatory conditions, including infections and concomitant medications such as corticosteroids, as well as the timing of blood sample collection, may influence SIRI values and introduce potential confounding. In addition, molecular subtypes were analyzed as composite categories rather than being stratified by individual biomarkers (ER, PR, HER2, and Ki-67), which may have obscured the independent contribution of each biomarker and introduced residual bias. Further research is needed to validate SIRI as a robust prognostic predictor through prospective, multicenter studies with standardized cutoff calibration. Longitudinal assessment of SIRI during treatment may provide additional prognostic value by capturing dynamic changes in systemic inflammation and immune status. Moreover, integrating SIRI with established clinicopathological factors, molecular subtypes, and genomic biomarkers could enhance prognostic stratification and support more individualized treatment decision-making.

Conclusion

Pre-treatment SIRI was associated with the presence of distant metastasis in breast cancer, supporting its potential as a practical, low-cost, and non-invasive prognostic biomarker. SIRI may be considered as an adjunct parameter in initial clinical assessment to support risk stratification. Further prospective multi-center studies are warranted to validate its clinical utility and determine an optimal cut-off before broader implementation.

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Conflict of Interests

The authors declare no conflicts of interest. The authors had full access to all study data and took responsibility for the integrity and accuracy of the analysis.

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