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# The preoperative systemic inflammation response index (SIRI) independently predicts survival in postmenopausal women with breast cancer

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## ABSTRACT

The recently developed preoperative systemic inflammation response index (SIRI) was reported as a useful biomarker that could predict survival in certain types of malignant tumors. However, the prognostic value of preoperative SIRI in postmenopausal breast cancer remains unclear. This study aimed to explore the relationship between SIRI and survival in postmenopausal patients with breast cancer. A total of 390 postmenopausal patients with breast cancer who underwent a mastectomy at Sun Yat-sen University Cancer Center were retrospectively studied. SIRI was based on peripheral neutrophil, monocyte, and lymphocyte counts, calculated as: neutrophil count × monocyte count/lymphocyte count. The best cut-off value for SIRI was determined using receiver operating characteristic curve analysis. Patients were divided into

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2 groups:Low SIRI < 0.54 and high SIRI > 0.54. High SIRI was significantly related to progesterone receptor status. Kaplan-Meier survival analysis showed that T stage, N stage, clinical stage, carcinoembryonic antigen, estrogen receptor, progesterone receptor, endocrinotherapy, and SIRI were significantly correlated with overall survival (OS). Multivariate analysis showed that SIRI could also independently predict OS. Preoperative SIRI may be a reliable predictor of OS in postmenopausal patients with operable breast cancer to provide personalized prognostication and to assist in the formulation of a clinical treatment strategy.



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## Introduction

Breast cancer is one of the most common female malignant tumors, which seriously affects women's health and can endanger their lives.[1] The risk of breast cancer increases with age; however, the degree of malignancy decreases with age, especially for postmenopausal patients, in whom the positive rate of hormone receptors is significantly higher; therefore, the prognosis of postmenopausal patients with breast cancer is somewhat better.[2-4] Postmenopausal patients include most of the elderly patients, many of whom have poor physical health and cannot tolerate the treatment toxicities of chemotherapy and radiotherapy. In recent years, great progress has been made in clinical and basic research on breast cancer. In addition to conventional therapies such as surgery, radiotherapy, and chemotherapy, the American Society of Clinical Oncology and European Society of Medical Oncology guidelines recommend that endocrine therapy should be given as a priority to patients with hormone receptor-positive breast cancer.[5,6] Gene expression features, such as MammaPrint and OncotypeDX, are increasingly used to provide prognostic information and to better select patients who might benefit from adjuvant chemotherapy. However, the high cost of these genetic tests is not conducive to their widespread use. Therefore, it is important to explore novel and convenient tools that can predict effectively the survival of postmenopausal patients and thus help to tailor treatment regimens for patients who are at high risk of worse prognosis.

Tumor-related inflammation plays an important role in the development and progression of cancer, and immune and inflammatory cells are also crucial components of the tumor microenvironment.[7-9] Recently, many clinical and basic studies have explored the relationship between the local immune response and systemic inflammation, cancer progression, and patient survival.[10-16] Those routine immune and inflammatory cells (such as neutrophils, monocytes, and lymphocytes) that are present and can be detected in systemic circulation may contribute to the invasion and metastasis of tumor cells.[17] A series of reports have indicated that leukocyte counts (including neutrophil), lymphocytes, and mononuclear cell counts, and acute-phase proteins (such as c-reactive protein) levels have a predictive value in breast cancer and other cancers.[18-21] Patients with an elevated neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio, and c-reactive protein level had a worse prognosis in operable or neoadjuvant chemotherapy breast cancer.[14,21,22] Neutrophils promote cell development and progression by secreting cytokines and chemokines to provide an appropriate microenvironment for tumor cells.[23] Tumor-associated macrophages (TAMs), which are derived from circulating monocytes, play a key role in the formation of the tumor microenvironment by promoting tumor progression and metastasis.[24] By modifying the factors secreted by neutrophils and TAMs, the stemness of tumor stem cells are affected, making tumor cells resistant to chemotherapy drugs.[16,25,26] Lymphocytes can induce cytotoxic cell death and inhibit tumor cell proliferation and migration, and thus play a key role in cancer immune surveillance and defense.[9]

The Systemic Inflammation Response Index (SIRI), based on peripheral neutrophil (N), monocyte (M), and lymphocyte (L) counts, may better reflect the balance between host in-

flammation and immune status. Qi et al first reported that SIRI could effectively predict the survival of patients with pancreatic cancer.[27] Similar results were found for patients with gastric adenocarcinoma, hepatocellular carcinoma, and thyroid carcinoma.[28-30] Meanwhile, hormone level can affect the immune status of the host, which may cause differences in immune status between premenopausal and postmenopausal patients. This difference in immune status may also affect the prognosis in breast cancer. However, the prognostic value of preoperative SIRI in postmenopausal patients with breast cancer has not been reported.

In the present study, we assessed the efficacy of preoperative SIRI to predict the overall survival (OS) in postmenopausal women with breast cancer.

## Patients and methods

### *Patients*

We retrospectively recruited 390 postmenopausal female patients who underwent surgery for invasive breast cancer from December 2010 to June 2012 at Sun Yat-sen University Cancer Center, Guangzhou, China. Histopathologic and clinical examination data were obtained for all patients. The inclusion criteria were as follows: (1) Female breast carcinoma and postmenopause; (2) Histopathologic examination confirmed the diagnosis of breast cancer and no distant metastasis; (3) Received surgery. The exclusion criteria were as follows: (1) Male breast carcinoma or female patients with distant metastasis; (2) Treatment with neoadjuvant chemotherapy or radiotherapy; (3) Acute and/or chronic inflammatory, hematological, or autoimmune diseases; (4) Use of immunosuppressive or anti-inflammatory medicines; and (5) Loss of complete laboratory data. Tumor staging was based on the seventh edition of the International Union Against Cancer Tumor Node Metastasis (TNM) classification system of breast cancer. This study was approved by the Research Ethics Committee of Sun Yat-sen University Cancer Center and all patients provided written informed consent.

### *Data collection and definition*

The primary preoperative laboratory data from within 3 days of the time of surgery and clinicopathologic data were collected from the patients' medical records. ER and PR positivity was defined as more than 10% positive cells in immunohistochemical staining. HER2-positivity was defined as a 3+ immunohistochemical staining result or 2+ immunohistochemical staining result confirmed by fluorescent in situ hybridization (FISH). SIRI was calculated using the following formula: SIRI = neutrophil count × monocyte count/lymphocyte count.

### *Follow-up*

The patients were followed up carefully by conducting an outpatient examination or a telephone interview. OS was defined as the time from the date of surgery to the date of death or final follow-up.

### *Statistical analysis*

Statistical analyses were performed using the SPSS 23.0 (IBM Crop., Armok, NY) and GraphPad Prism 6.0 software (GraphPad, La Jolla, CA). The optimal cut-off value for SIRI was calculated

**Table 1**
Clinicopathologic features and the association of SIRI with clinicopathologic characteristics in 390 postmenopausal patients with breast cancer.

| Feature | Total (n = 390) | SIRI value | | *P* |
|---|---|---|---|---|
| | | Low | High | |
| Age (y) | | | | |
| ≥60 | 243 (62.3%) | 145 (59.7%) | 98 (40.3%) | 0.095 |
| <60 | 147 (37.7%) | 75 (51.0%) | 72 (49.0%) | |
| Histologic type | | | | |
| Invasive ducal carcinoma | 356 (91.3%) | 199 (55.9%) | 157 (44.1%) | 0.510 |
| Others | 34 (8.7%) | 21 (61.8%) | 13 (38.2%) | |
| T classification | | | | |
| 1 | 139 (35.6%) | 84 (60.4%) | 55 (39.6%) | 0.261 |
| 2 | 210(53.8%) | 116 (55.2%) | 94 (44.8%) | |
| 3 | 20 (5.1%) | 12 (60.0%) | 8 (40.0%) | |
| 4 | 21 (5.4%) | 8 (38.1%) | 13 (61.9%) | |
| N classification | | | | |
| 0 | 201(51.5%) | 115 (57.2%) | 86 (42.8%) | 0.960 |
| 1 | 102 (26.2%) | 58 (56.9%) | 44 (43.1%) | |
| 2 | 51 (13.1%) | 28 (54.9%) | 23 (45.1%) | |
| 3 | 36 (9.2%) | 19 (52.8%) | 17 (47.2%) | |
| Clinical stage | | | | |
| I | 94 (24.1%) | 60 (63.8%) | 34 (36.2%) | 0.244 |
| II | 200 (51.3%) | 109 (54.5%) | 91(45.5%) | |
| III | 96 (24.6%) | 51 (53.1%) | 45 (46.9%) | |
| ER | | | | |
| Negative | 172 (44.1%) | 62 (50.8%) | 60 (49.2%) | 0.110 |
| Positive | 208 (53.3%) | 153 (59.5%) | 104 (40.5%) | |
| PR | | | | |
| Negative | 172 (44.1%) | 88 (51.2%) | 84 (48.8%) | **0.042** |
| Positive | 208 (53.3%) | 128 (61.5%) | 80 (38.5%) | |
| HER2 | | | | |
| Negative | 240 (61.5%) | 137 (57.1%) | 103 (42.9%) | 0.645 |
| Positive | 112 (28.7%) | 61 (54.5%) | 51 (45.5%) | |
| CEA | | | | |
| Negative | 331 (84.9%) | 192 (58.0%) | 139 (42.0%) | 0.755 |
| Positive | 45 (11.5%) | 25 (55.6%) | 20 (44.4%) | |
| CA153 | | | | |
| Negative | 332 (85.1%) | 197 (59.3%) | 135 (40.7%) | 0.058 |
| Positive | 45 (11.5%) | 20 (44.4%) | 25 (55.6%) | |
| Surgery | | | | |
| Radical surgery | 17 (4.4%) | 8 (47.1%) | 9 (52.9%) | 0.687 |
| Modified radical surgery | 347 (89.0%) | 197 (56.8%) | 150 (43.2%) | |
| Breast conserving surgery | 25 (6.4%) | 15 (60.0%) | 10 (40.0%) | |
| Adjuvant chemotherapy | | | | |
| Yes | 292 (74.9%) | 167 (57.2%) | 125 (42.8%) | 0.591 |
| None | 98 (25.1%) | 53 (54.1%) | 45 (45.9%) | |
| Adjuvant radiotherapy | | | | |
| Yes | 80 (20.5%) | 39 (48.8%) | 41 (51.3%) | 0.121 |
| None | 310 (79.5%) | 181 (58.4%) | 129 (41.6%) | |
| Endocrinotherapy | | | | |
| Yes | 204 (52.3%) | 119 (58.3%) | 85 (41.7%) | 0.423 |
| None | 186 (47.7%) | 101 (54.3%) | 85 (45.7%) | |

CA153, cancer antigen 15-3; CEA, carcinoembryonic antigen; ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; PR, progesterone receptor; SIRI, systemic inflammation response index.

using receiver operating characteristic curve analysis using the highest Youden's index (sensitivity + specificity − 1) to predict OS. The associations between SIRI and clinicopathologic features were analyzed using Pearson's $\chi 2$ test or Fisher's exact test. Survival curves were calculated using the Kaplan-Meier method and compared via the log-rank test. Univariate and multivariate analyses were performed using Cox's proportional hazards models. Two-sided $P$ values $< 0.05$ were considered statistically significant.

## Results

### *Patient characteristics*

We enrolled 390 patients into this retrospective study and their clinical characteristics are list in Table 1. All variables were measured within 3 days before surgery as the baseline data. The median patient age was 68 years (range 49-87 years), and the median follow-up period was 65.5 months (range 0.9-95.9 months). The median OS was 65.8 months, while the 5-year OS rate was 88.5%. At the final follow-up, 55 (14.1%) patients had died and 335 (85.9%) were still alive.

### *Relationship between SIRI and clinicopathologic characteristics*

The optimal cut-off of SIRI was calculated using receiver operating characteristic curve analysis for OS, and the optimal cut-off value was 0.54 with an area under the curve of 0.600 and the highest Youden's index of 0.201 (sensitivity: 0.665; specificity: 0.536). Patients were grouped using the optimal cut-off SIRI value of 0.54 (low, $<0.54$; high, $>0.54$) and 220 patients showed low SIRI values, whereas 170 patients had high SIRI values. As shown in Table 1, high SIRI values were significantly associated with progesterone receptor status ($P=0.042$).

### *Prognostic value of SIRI*

The median OS, RFS, DMFS, and DFS for the entire cohort was 65.8, 65.2, 64.3, and 64.4 months, respectively and patients with elevated SIRI scores had a median OS of 62.8 months, i.e., they survived for shorter time than those with lower SIRI scores, who had a median OS of 69.2 months ($P=0.002$) (Fig. 1). Patients with high SIRI had a median OS of 62.8 months significantly shorter than those with low SIRI had a median OS of 69.2 months ($P=0.002$, Fig. 1A). Patients with high SIRI had a median RFS, DMFS and DFS of 62.8, 61.5, 61.2 months, which is shorter but not significantly than those with low SIRI had a median RFS, DMFS and DFS of 68.9, 67.4, 67.7 months ($P=0.677$, Fig. 1B; $P = 0.443$, Fig. 1C; $P=0.298$, Fig. 1D).

### *Univariate and multivariate Cox regression analysis for OS*

Univariate Cox regression analysis revealed that T stage, N stage, clinical stage, estrogen receptor status, carcinoembryonic antigen, endocrinotherapy, and SIRI all showed significant associations with survival. Multivariate survival analysis revealed that SIRI could independently predict OS ($P=0.008$; Table 2).

## Discussion

Women with breast cancer and with different menstrual statuses have different degrees of tumor malignancy; tumor differentiation; and estrogen receptor, progesterone receptor, human epidermal growth factor receptor-2, and Ki-67 status.[31,32] There are also differences in tumor molecular subtypes, pathologic type, histologic grading, and clinical pathologic staging among women with different menstrual statuses.[33] Although the specificity of postmenopausal breast cancer is well known, few clinical tumor markers can effectively predict the prognosis of such patients. In addition to surgery, radiotherapy, and chemotherapy, the American Society of Clinical Oncology and European Society of Medical Oncology guidelines recommend that endocrine therapy should be given as a priority to patients with hormone receptor-positive breast cancer.[5,6] However, there is no consensus on the specific treatment regimen for postmenopausal

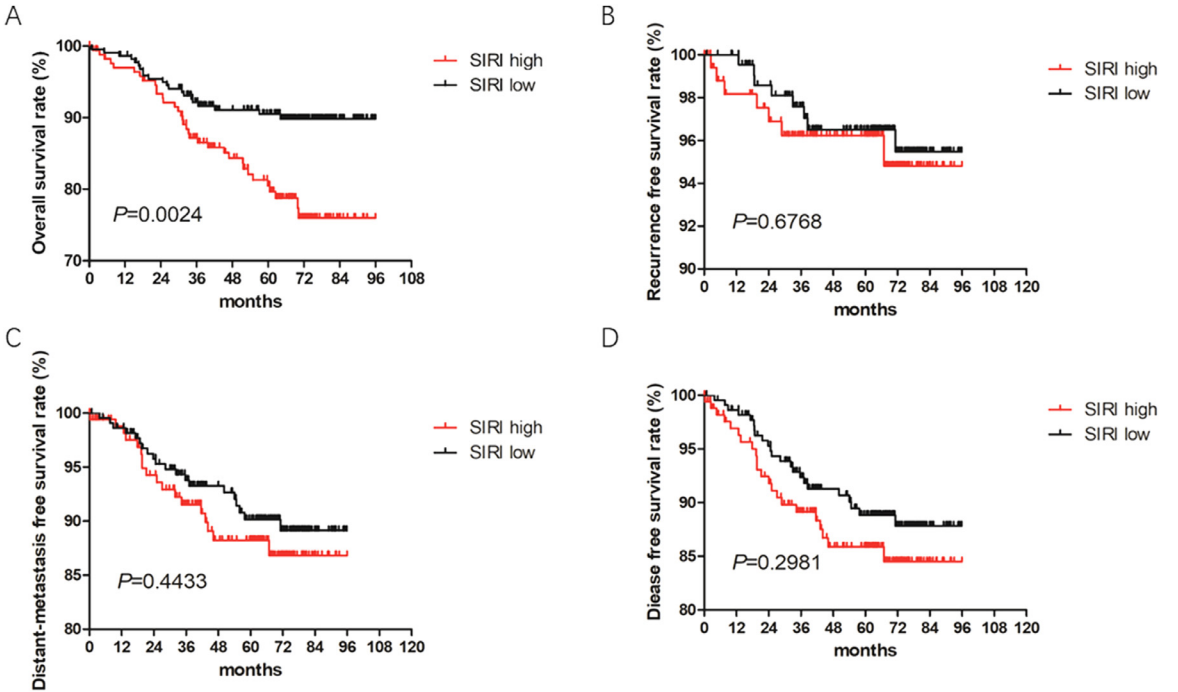


**Fig. 1.** Kaplan-Meier survival curves for overall survival (OS), recurrence free survival (RFS), distant-metastasis free survival (DMFS) and disease free survival (DFS) according to systemic inflammation response index (SIRI) scores in postmenopausal patients with breast cancer.

**Table 2**
Univariate and multivariate Cox regression analysis of the associations between clinicopathologic characteristics and overall survival in postmenopausal patients with breast cancer.

| Feature | Univariate analysis | | Multivariate Cox regression analysis | |
|---|---|---|---|---|
| | Regression coefficient (SE) | *P* | Hazard ratio (95%CI) | *P* |
| Age (y) | −0.308 (0.292) | 0.291 | | |
| Histologic type | −1.664 (1.009) | 0.099 | | |
| T stage | 0.614 (0.142) | **<0.001** | 1.835(0.874-3.851) | 0.109 |
| N stage | 0.851 (0.119) | **<0.001** | 5.694(2.634-12.312) | **<0.001** |
| ER | −0.564 (0.281) | **0.045** | 0.827(0.419-1.634) | 0.585 |
| PR | −0.445 (0.276) | 0.107 | | |
| HER2 | 0.538 (0.287) | 0.061 | | |
| CEA | 0.910 (0.330) | **0.006** | 1.386(0.696-2.761) | 0.353 |
| CA153 | 0.444 (0.367) | 0.226 | | |
| Surgery | 0.153 (0.402) | 0.703 | | |
| Adjuvant chemotherapy | 0.674 (0.382) | 0.078 | | |
| Adjuvant radiotherapy | 0.520 (0.292) | 0.075 | | |
| Endocrinotherapy | −0.668 (0.276) | **0.015** | 0.549(0.277-1.089) | **0.086** |
| SIRI | 0.820 (0.278) | **0.003** | 2.175(1.228-3.853) | **0.008** |

CA153, cancer antigen 15-3; CEA, carcinoembryonic antigen; CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; PR, progesterone receptor; SE, standard error of the mean; SIRI, systemic inflammation response index.
Significant results are shown in bold font.

patients with breast cancer, and clinicians often determine the treatment of such patients according to molecular classification and gene expression features, such as MammaPrint and OncotypeDX, and thus determine whether the prognosis is good or not. However, these tests are time-consuming and expensive. Therefore, there is an urgent need to find convenient, low-cost, and reliable tumor markers to predict the prognosis of postmenopausal patients with breast cancers.

Cancer-related inflammation is recognized as the seventh hallmark of cancer, and recent studies have shown that local immune responses and systemic inflammation affect the survival and prognosis of patients with cancer by promoting the development and progression of tumors.[7,8] The predictive value of circulating neutrophils in many cancers (including breast cancer) is reliable, either as an independent measure or as part of the NLR.[14,34] It has been consistently demonstrated that patients with elevated peripheral absolute neutrophil count or NLR present decreased survival in many cancers, including breast cancer.[35] Similarly, poor survival and increased tumor progression are reported for patients presenting with high numbers of circulating monocytes or monocyte-lymphocyte ratio.[21] In the present study, we found that SIRI could predict the survival of postmenopausal patients with breast cancer who underwent surgery. SIRI, as a convenient, easy to obtain, low-cost, and noninvasive prognostic indicator, can be used as a supplement to existing methods, such as molecular classification, pathologic characteristics, and TNM stage, to better predict the prognosis of postmenopausal patients with breast cancer and allows clinicians to screen patients with potentially poor outcomes for more aggressive therapy regimens.

The physiological and pathologic functions of neutrophils, monocytes, and lymphocytes may partially explain the mechanisms by which SIRI has prognostic significance in postmenopausal patients with breast cancer Neutrophils help cancer cells evade immune surveillance by promoting their invasion, proliferation, and metastasis. Monocytes, especially TAMs, which are derived from circulating monocyte populations, exert a significant influence on the tumor microenvironment by promoting tumor progression and metastasis.[23] In addition, some studies have shown that by modifying the factors secreted by neutrophils and TAMs, the stem cell properties of tumor stem cells can be affected, thus affecting their sensitivity to chemotherapy drugs.[26] Lymphocytes play an important role in tumor immune monitoring and defense by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration.[9] Therefore, the levels of these

cells indicate the host's immune response to malignant tumors. These above reasons may account for higher SIRI values patients present with worse survival.

This study may help to better understand the relationship between immunity, inflammation, and cancer prognosis, and may also provide guidance for the development of more suitable individualized and precise treatment programs for postmenopausal patients with breast cancer in the future. Patients with a potentially poor prognosis, that is, patients with higher SIRI values, may be prescribed more aggressive therapy regimens: (1) Endocrinotherapy should be conducted as early as possible and preoperative neoadjuvant endocrine therapy is recommended. (2) Appropriate prolongation of endocrinotherapy to 10 years or even lifetime use until disease progression. (3) Timely use of complementary immunotherapy and anti-inflammatory drugs, such as thymosin, herceptin, and aspirin.

This study has several limitations. First, as a single center retrospective study with a relatively small sample size, the conclusions may be biased. Second, SIRI has been shown to independently predict the prognosis of postmenopausal patients with breast cancer; however, its sensitivity and specificity are not high, and further prospective studies are needed to determine the appropriate cut-off value. Third, SIRI's prognostic value in premenopausal patients with breast cancer remains unclear and further research is needed. Furthermore, the exact reason why PR and SIRI were statistically significantly associated was unclear and one of the most likely reasons may be selection bias, and large prospective trails are needed for verification.

In summary, the present study reported the significance of preoperative SIRI in the prognosis of breast cancer. The current findings confirmed SIRI as a promising biomarker to predict the clinical outcome of postmenopausal patients with breast cancer. Patients with high SIRI values present a poor prognosis.

## Authors' contributions

Conceptualization: XH HXL; Methodology: XH XH; Software: XH ZQL; Validation: ZQL; Formal analysis: XH HXL; Investigation: ZQL XH JPD; Resources: HXL WWZ; Data curation: XH HXL LG; Writing (original draft preparation): XH; Writing (review and editing): all authors; Visualization: XH ZYH LG; Supervision: WWZ HXL; Project administration: HXL; Funding acquisition: LG HXL WWZ ZYH. All authors approve the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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