Original Article

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Pathology Section

Systemic Immune Inflammatory Index and Systemic Inflammatory Response Index in Invasive Ductal Carcinoma of the Breast and their Association with Molecular Types, Grade and Stage of Disease: A Cross-sectional Study

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ABSTRACT

Introduction: Breast cancer is the most frequently encountered malignant tumour in women around the world with high incidence and mortality rates worldwide. The concept of being able to prognosticate breast cancer based on routine peripheral blood examinations is attractive given the ease of access, replicability, and lower cost.

Aim: To estimate the Systemic Immune-inflammatory Index (SII) and Systemic Inflammatory Response Index (SIRI) in invasive ductal carcinoma of breast and to study association between SII and SIRI with prognostic parameters such as molecular subtypes, Grade and Stage of the disease.

Materials and Methods: This retrospective cross-sectional analytical study was conducted at Departments of Pathology and Surgical Oncology, Sri Devaraj Urs Medical college, Tamaka, Karnataka, India, from February 2024 to August 2024 it included 90 histopathologically confirmed cases of invasive ductal carcinoma of the breast diagnosed between January 2018 and December 2020. Clinicopathological data such as age, tumour grade, stage, and molecular subtype were obtained from medical records. Neutrophil, lymphocyte, monocyte, and platelet counts were obtained from case files. The SII and SIRI were calculated using standard formulas. Optimal cut-off values were derived using Receiver Operating Characteristic (ROC) curve analysis, and patients were categorised into high and low index groups. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 22.0. Associations between inflammatory indices and prognostic parameters were assessed using the Chi-square test, with $p<0.05$ considered statistically significant.

Results: A total of 90 patients with invasive ductal carcinoma of the breast were included in the study. Based on ROC analysis, the cut-off values for SII and SIRI were 568.83 and 0.831, respectively. High SII levels showed a statistically significant association with histological grade ($p=0.002$). However, no significant association was observed between SII and tumour stage ($p=0.235$) or molecular subtype ($p=0.770$). Similarly, elevated SIRI levels were significantly associated with histological grade ($p=0.013$) and tumour stage ($p=0.022$). No significant association was observed between SIRI and molecular subtypes ($p=0.734$).

Conclusion: Systemic inflammatory indices such as the SII and SIRI represent accessible, inexpensive, and non invasive tools that may aid in prognostic assessment and risk stratification in patients with invasive ductal carcinoma of the breast. Their evaluation using routine peripheral blood parameters highlights the potential clinical utility of inflammation-based biomarkers in the overall management and prognostication of breast cancer.

Keywords: Breast cancer, Peripheral blood indices, Prognostic biomarkers, Systemic inflammation

INTRODUCTION

Breast cancer is the most frequently encountered malignant tumour in women around the world with high incidence and mortality rates worldwide. In 2022, an estimated 2.3 million new cases of breast cancer were diagnosed worldwide, with approximately 670,000 deaths, making it the most commonly diagnosed cancer globally and the leading cause of cancer-related mortality among women. Breast cancer continues to be a major and growing public health concern in India [1]. According to Global Cancer Observatory (GLOBOCAN) 2022, India recorded 192,020 new breast cancer cases and 98,337 deaths, accounting for approximately 14.2% of all female cancers and 10.9% of all cancer related deaths, thereby ranking breast cancer as the most common malignancy among Indian women. The age-standardised incidence rate has shown a consistent upward trend over the past three decades, reflecting the increasing disease burden [2]. Breast cancer is also a significant health concern in the southern state of Karnataka, India, with a high incidence rate reported in several districts. According to data from the National Cancer Registry Program of India, the age-adjusted incidence rate of breast cancer in Karnataka was 27.8 per 100,000 women in 2020 [3]. It is also important to note that breast cancer in India is often diagnosed at an advanced stage, which makes it more difficult to treat and results in higher mortality rates. Breast cancer is also a serious health concern in Kolar, a district located in the southern state of Karnataka, India and is the third most common cancer among women in Kolar, accounting for 10.8% of all cancers in women [4]. Hence, important measures are needed to address the challenges posed by breast cancer in Kolar and other parts of India.

In recent years, many researchers have paid attention to inflammation and found that cancer-related inflammation played an essential role in cancer development and prognosis [5]. While lymphocytes are

cytotoxic to cancer cells, neutrophils are known to have a positive impact on cancer progression [6]. The latest evidence also suggests that a similar tumour-inflammation relationship exists for breast cancer, indicating that quantifying the inflammatory response may be useful in treating and prognosticating breast cancer [7]. Breast cancer is currently diagnosed by a combination of pathological assessments of tissue samples taken via Core Needle Biopsy (CNB) and various imaging modalities including breast ultrasound, mammography, and Magnetic Resonance Imaging (MRI) [8]. Nevertheless, the concept of being able to prognosticate breast cancer based on routine peripheral blood examinations is attractive given the ease of access, replicability, and lower cost.

The SII is an indicator that is based on neutrophil, lymphocyte, and platelet counts, and defined as platelet × neutrophil/lymphocyte, a potential indicator capable of establishing balance between inflammatory and immune status in the host [9]. SIRI can be determined as SIRI = neutrophil count × monocyte count/lymphocyte count and emphasises the critical role of maintaining a balance between pro-inflammatory and anti-inflammatory factors in tumour biology [10].

The SII has been investigated in various cancers, including nasopharyngeal carcinoma, prostate cancer, colorectal cancer, pancreatic cancer, gastric cancer, and hepatocellular carcinoma [11]. However, the role of SII in breast cancer patients has not been well understood. Similarly many previous studies have explored the significance of the SIRI in predicting breast cancer prognosis, but no consistent findings have been obtained [12]. Therefore, this research was focused on exploring the clinical significance of SII and SIRI in invasive ductal carcinoma breast patients. And the objectives were to estimate the SII and SIRI in Infiltrating ductal carcinoma of breast.; to determine the association of SII and SIRI with prognostic parameters such as molecular subtypes, Grade and Stage of infiltrating ductal carcinoma of breast.

MATERIALS AND METHODS

This retrospective cross-sectional analytical study was conducted in the Departments of Pathology and Surgical Oncology at Sri Devaraj Urs Medical College, Tamaka, Kolar, Karnataka, India, from February 2024 to August 2024. Ethical clearance was obtained from the Central Ethics committee. IEC No.: SDUMC/KLR/IEC/582/2023-24 Data were obtained from the case records of patients diagnosed with breast cancer in the Department of Pathology at Sri Devaraj Urs Medical College for the period from January 2018 to December 2020. Relevant haematological and laboratory parameters were extracted from medical records for analysis.

Sample size: The sample size was determined based on the Institutional case load during the study period. Approximately, 90 eligible cases of infiltrating ductal carcinoma were identified from records corresponding to the study period. All consecutive cases meeting the predefined inclusion and exclusion criteria were included, yielding a final sample size of 90. As this was a hospital-based retrospective study, a formal prevalence based sample size calculation was not performed, and consecutive convenience sampling was used.

Inclusion criteria: Inclusion criteria comprised histopathologically confirmed cases of invasive ductal carcinoma of the breast with available pre-treatment Complete Blood Count (CBC) data and complete clinicopathological details.

Exclusion criteria: It included patients with other histological types of breast carcinoma, those who had received prior chemotherapy and radiotherapy.

Study Procedure

Data collection and laboratory analysis: Relevant demographic, clinical, and histopathological data, including tumour size, stage according to American Joint Committee on Cancer (AJCC) 8th Edition [13], histopathological grade assessed using Modified Bloom-Richardson's Histological Grading System [13], lymph node status, and hormonal biomarker status {Oestrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor (HER2/neu) Ki-67}, were systematically retrieved from the departmental archives. Pre-treatment peripheral blood samples were collected from each patient and analysed for CBC using an automated haematology analyser. The following haematological indices were used to calculate the SII and SIRI:

SII = (Platelet count × Neutrophil count)/Lymphocyte count [9].

SIRI = (Neutrophil count × Monocyte count)/Lymphocyte count [10].

The critical optimal threshold values of related variables were identified utilising ROC curves similar to study by Ling X and Zhu M et al., [11,12].

The Receiver Operating Characteristics (ROC) curve analysis was performed to determine optimal cut-off values of SII and SIRI for predicting adverse prognostic categories such as grade, stage, and molecular classification where applicable. ROC curves were generated using a non parametric method with reference curve and inclusion of all cut-off points. Area Under the Curve (AUC) and ROC coordinate tables (sensitivity and 1- specificity) was obtained. The optimal thresholds were selected using the Youden index from the ROC coordinate tables by identifying the point with the highest combined sensitivity and specificity.

For SII, the selected cut-off showed a sensitivity of 67.57% and a specificity of 50.94%, with an optimal cut-off value of 568.83. For SIRI, the chosen cut-off demonstrated a sensitivity of 37.84% and a specificity of 88.68%, with an optimal cut-off value of 0.831. Based on ROC analysis, the cut-off values derived were 568.83 for SII and 0.831 for SIRI, and cases were categorised into high and low index groups accordingly.

Based on the cut-off values of SII and SIRI, patients were divided into a high-SII group (SII ≥ 568.83), a low-SII group (SII <568.83), a high-SIRI group (SIRI >0.831), and a low-SIRI group (SIRI ≤0.831). Receiver Operating Characteristic (ROC) analysis was performed to determine optimal cut-off values for SII and SIRI (Table/Fig-1). The corresponding ROC curves are illustrated in (Fig-2).

STATISTICAL ANALYSIS

All data were entered into Microsoft Excel and analysed using SPSS version 22.0 software. Categorical variables such as tumour grade, stage, and ER, PR, HER2/Neu status were presented as percentages. ROC curve analysis was performed to evaluate the discriminatory ability of SII and SIRI for prognostic categories and to derive optimal cut-off values. ROC curves were generated using a non parametric method, and the AUC with 95% confidence intervals was calculated. Cut-off values were derived using the Youden index from the ROC coordinate tables. The association of SII and SIRI with tumour grade, stage, and molecular subtype was assessed using the Chi-square (χ^2) test where expected cell counts were adequate, and Fisher's-exact test was applied where expected counts were less than 5. A p-value<0.05 was considered statistically significant.

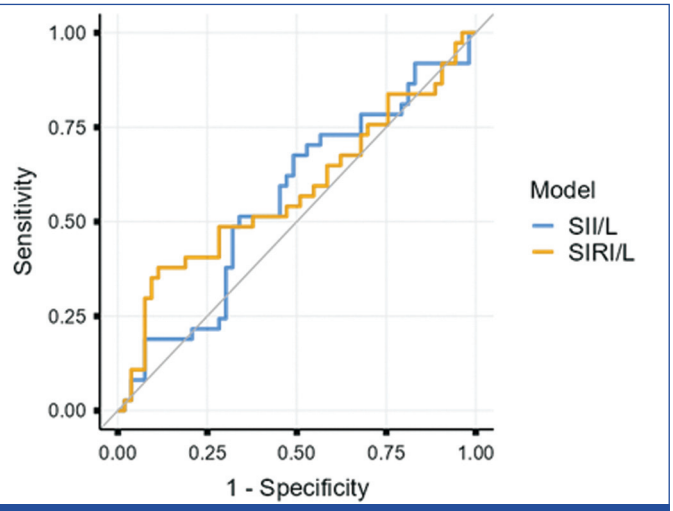
RESULTS

A total of 90 patients with histopathologically confirmed invasive ductal carcinoma of the breast were included in the study. All patients were females, with ages ranging from 31 to 82 years; the majority were aged ≤ 55 years 55 cases (61.1%), while 35 cases (38.9%) were older than 55 years.

Based on histological grading, 56 cases (62.2%) were Grade 1 (Well-differentiated), 24 cases (26.7%) were Grade 2 (Moderately-differentiated), and 10 cases (11.1%) were Grade 3 (Poorly-differentiated) tumours [Table/Fig-3]. Clinicopathological staging

Variables	AUC (95% CI)	Standard Error	p-value	Optimal cut-off (Youden Index)	Sensitivity (%)	Specificity (%)
SII	0.559 (0.437 – 0.682)	0.0625	0.342	568.83	67.57	50.94
SIRI	0.579 (0.453 – 0.705)	0.0644	0.218	0.831	37.84	88.68

[Table/Fig-1]: ROC analysis for determination of cut-off values of SII and SIRI.



[Table/Fig-2]: ROC curves showing the predictive performance of SII and SIRI for adverse prognostic categories in invasive ductal carcinoma of the breast.

Parameters	Category	n (%)
Age	≤55 years	55 (61.1)
	>55 years	35 (38.9)
Grade	1	56 (62.2)
	2	24 (26.7)
	3	10 (11.1)
Stage	I	2 (2.2)
	II	51 (56.7)
	III	35 (38.9)
	IV	2 (2.20)
ER	Positive	47 (52.2)
	Negative	43 (47.8)
PR	Positive	44 (48.9)
	Negative	46 (51.1)
HER2/neu	Positive	21 (23.3)
	Negative	69 (76.7)
Ki-67	<14%	41 (45.6)
	>14%	49 (54.4)
Molecular Classification	Luminal A	33 (36.7)
	Luminal B	19 (21.1)
	HER2-positive	11 (12.2)
	TNBC	27 (30.0)

[Table/Fig-3]: Clinicopathological characteristics of breast cancer patients (N=90). *Chi-square test

revealed that most patients presented with Stage II disease 51 cases (56.7%), followed by Stage III 35 cases (38.9%), while Stage I and Stage IV disease were observed in 2 cases each (2.2%).

Hormone receptor analysis showed oestrogen receptor positivity in 47 cases (52.2%) and progesterone receptor positivity in 44 cases (48.9%). HER2/neu positivity was observed in 21 cases (23.3%), while Ki-67 index >14% was noted in 49 cases (54.4%). Molecular classification revealed Luminal A subtype in 33 cases (36.7%), Luminal B in 19 cases (21.1%), HER2-positive subtype in 11 cases (12.2%), and triple-negative breast cancer in 27 cases (30.0%) [Table/Fig-4].

Estimation of SII and SIRI

Using pre-treatment peripheral blood counts, the SII and SIRI were calculated for all cases. Patients were categorised into high and low SII and SIRI groups using ROC curve derived cut-off values. The optimal cut-off for SII was 568.83 (AUC 0.559; sensitivity 67.57%; specificity 50.94%), and for SIRI was 0.831 (AUC 0.579; sensitivity 37.84%; specificity 88.68%) based on the Youden index [Table/Fig-4,5].

Association of SII and SIRI with Tumour Stage

When analysed against clinicopathological stage, SII did not demonstrate a statistically significant association with tumour stage (p=0.235). However, elevated SIRI levels showed a statistically significant association with higher tumour stage (p=0.022).

Association of SII and SIRI with Tumour Grade

SII showed a statistically significant association with histological grade (p=0.002). Similarly, SIRI also demonstrated a statistically significant association with tumour grade (p=0.013).

Association of SII and SIRI with Molecular Subtypes

Analysis across molecular subtypes revealed no significant association between SII and molecular classification (p=0.770). Similarly, SIRI levels were not significantly associated with molecular subtypes (p=0.734).

DISCUSSION

Breast cancer is a very common malignancy in females whose incidence has surpassed that of lung cancer [1]. With advancements in tumour biology, several studies have highlighted the role of inflammation in tumour initiation, progression and metastasis. Inflammation plays a direct role in altering the tumour microenvironment, fostering malignant transformation, invasion and metastasis. Several studies have shown that inflammatory markers within tumour microenvironment can help predict breast cancer progression and prognosis, with inflammatory response serving as a crucial indicator of breast cancer outcomes [11,12]. This emphasises on the significance of inflammation in clinical disease assessment and treatment planning.

Thus, understanding the relationship between common peripheral blood markers and breast cancer prognosis holds significant research value. Neutrophils contribute to tumour progression by promoting the secretion of Interleukin-6 (IL-6), Arginase-1 (Arginase-1), and Vascular Endothelial Growth Factor (VEGF) [14]. Lymphocytes play a vital role in tumour immune surveillance, suppressing tumour growth and metastasis by activating Natural Killer (NK) cells and macrophages [15].

Monocytes can differentiate into Tumour-Associated Macrophages (TAMs), which are recruited into the tumour microenvironment by tumour-secreted chemokines. Certain TAMs promote angiogenesis, immune evasion, and tumour progression by secreting cytokines and growth factors [16]. SII and SIRI have emerged as significant markers due to their reflection of the body's inflammatory and immune status, both of which are increasingly recognised as critical factors in cancer prognosis [17,18]. The present study investigates the association between systemic inflammatory indices, specifically the SII and SIRI, with the histological grade, clinicopathological stage and molecular classification in invasive ductal carcinoma of the breast.

Association of SII and SIRI with tumour grade and stage: The findings of the present study suggest that high SIRI (SIRI >0.831) was significantly associated with both tumour stage (p=0.022) and tumour grade (p=0.013) in cases of invasive ductal carcinoma of the breast.

In contrast, high SII (SII ≥568.83) demonstrated a statistically significant association with histological grade (p=0.002), but did not show a significant association with tumour stage (p=0.235). Neither SIRI nor SII demonstrated a significant association with molecular classification. These results indicate that SIRI may serve as a marker

Clinicopathological variables	Category	Low SII (n=39) SII <568.83	High SII (n=51) SII ≥568.83	Total	Test used	p-value
Histological grade	Grade I	32	24	56	χ^2 (df=2)	0.002
	Grade II	4	20	24		
	Grade III	3	7	10		
Tumour stage	Stage I	1	1	2	Fisher's-exact	0.235
	Stage II	26	25	51		
	Stage III	12	23	35		
	Stage IV	0	2	2		
Molecular classification	Luminal A	14	19	33	Fisher's-exact	0.770
	Luminal B	10	9	19		
	HER2-positive	5	6	11		
	TNBC	10	17	27		

[Table/Fig-4]: The association of the level of SII with clinicopathological characteristics.
*Chi-square test, Fisher's-exact

Clinicopathological variables	Category	High SIRI (SIRI >0.831) (n=70)	Low SIRI SIRI ≤0.831 (n=20)	Total	Test used	p-value
Histological grade	Grade I	45	11	56	Fisher's-exact	0.013
	Grade II	21	3	24		
	Grade III	4	6	10		
Tumour stage	Stage I	2	0	2	Fisher's-exact	0.022
	Stage II	45	6	51		
	Stage III	21	14	35		
	Stage IV	2	0	2		
Molecular classification	Luminal A	27	6	33	Fisher's-exact	0.734
	Luminal B	13	6	19		
	HER2-positive	9	2	11		
	TNBC	21	6	27		

[Table/Fig-5]: The association of the level of SIRI with clinicopathological characteristics.
*Fisher's-Exact

of disease advancement in relation to both stage and grade, while SII appears to be associated particularly with tumour differentiation rather than clinical stage.

Similar findings have been reported in previous studies. Hua X et al., observed that higher preoperative SIRI was significantly associated with poor survival, thereby affirming its prognostic value. They further reported that increased SIRI levels, both before and after surgery, predicted an unfavourable prognosis in patients with operable breast cancer. This underscores the importance of SIRI as a prognostic marker [10]. Zhu M et al., also demonstrated that elevated SIRI levels correlate with poor outcomes in breast cancer and other malignancies [12].

By contrast, evidence regarding the prognostic significance of SII is less consistent. While some studies have shown that elevated SII is associated with poorer survival and disease progression [18]. Our study demonstrated a significant association of SII with histological grade but not with tumour stage or molecular classification. This discrepancy may reflect variations in study design, patient population or sample size.

Association of SII and SIRI with molecular classification: This study does not show significant association of SIRI and SII with molecular subtypes suggesting that these inflammatory indices may not be useful for predicting breast cancer molecular subtypes. This finding is consistent with previous studies, which showed that these indices of systemic inflammation have great value for predicting overall prognosis but do not correlate with specific molecular subtypes [10].

Clinical implications: The findings of the current study have significant therapeutic value for the treatment of invasive ductal carcinoma of the breast. SIRI may be a helpful index biomarker in clinical practice as it showed statistically significant correlation with both tumour stage and tumour grade. SII also demonstrated a significant association with histological grade, although it did not show a significant correlation with tumour stage.

SIRI and SII are inexpensive and non invasive tools for oncologists as they are simple to collect via standard blood testing. More investigation is necessary to confirm whether these inflammatory indices have predictive value in directing targeted therapy, as there is no significant relationship between them and molecular classification.

Limitation(s)

The present study has several limitations. The sample size was relatively small, which limits the generalisability of the findings. Larger and multicentre studies are essential to validate these results in a broader patient population. This was a cross-sectional study. Longitudinal studies with follow-up data would provide better insights into the prognostic value of SII and SIRI over time. The study did not take into account potential confounding factors such as co-morbidities, lifestyle factors, or genetic predispositions that may influence inflammatory markers. Future research should incorporate multivariate analyses to adjust for these confounders.

CONCLUSION(S)

The present study highlights the potential role of systemic inflammatory markers, particularly SIRI and SII, in invasive ductal carcinoma of the breast. SIRI demonstrated a significant association with both tumour stage and histological grade, while SII showed a significant association with histological grade but not with tumour stage. No significant correlation was observed with molecular subtypes for either index. These findings suggest that SIRI and SII may serve as valuable, cost-effective, and non invasive prognostic tools for assessing tumour differentiation and disease advancement, thereby aiding in risk stratification in breast cancer patients.

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