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RESEARCH ARTICLE

Prognostic Significance of Pre-treatment Systemic Immune Inflammation Index (SIII) in Patients with Advanced Epithelial Ovarian Cancer Treated with Neoadjuvant Chemotherapy

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Abstract

Introduction: The Systemic Immune-Inflammation Index (SIII), derived from peripheral blood parameters, reflects the balance between host inflammation and immune response. Although its prognostic value has been demonstrated in several malignancies, its role in epithelial ovarian cancer treated with neoadjuvant chemotherapy (NACT) remains unclear. The primary objective of this study was to evaluate the prognostic significance of pre-treatment SIII in patients with advanced epithelial ovarian cancer undergoing NACT. **Materials and Methods:** We retrospectively analysed patients with FIGO stage II-IV epithelial ovarian cancer treated with NACT followed by interval debulking surgery (IDS) or completion surgery at Dr. B. Borooah Cancer Institute, Guwahati, India, between 1 January 2019 and 30 June 2023. Pre-treatment SIII was calculated as (platelet count × neutrophil count)/lymphocyte count. Patients were stratified into high- and low-SIII groups based on a receiver operating characteristic (ROC)-derived cut-off determined using the Youden Index for overall survival (OS). Progression-free survival (PFS) and OS were evaluated using Kaplan-Meier analysis and Cox proportional hazards regression. A two-sided p-value <0.05 was considered statistically significant. **Results:** Among 284 patients, the median age was 52 years, and high-grade serous carcinoma was present in 76%. With a median follow-up of 41 months, median PFS was 19.7 months versus 10.5 months (p<0.001), and median OS was 37.8 months versus 21.4 months (p<0.001), in the low- and high-SIII groups, respectively. On multivariable analysis, after adjusting for age, FIGO stage, and residual disease following IDS, high SIII remained an independent predictor of poor PFS (HR 2.03; 95% CI 1.36-3.04; p<0.001). High SIII also independently predicted worse OS (HR 2.42; 95% CI 1.52-3.85; p<0.001). Patients with high SIII more frequently experienced progression at multiple sites (27.8% vs. 16.7%) and had higher rates of progression involving ascites (10.3% vs. 4.6%), pleural/lung metastases (7.1% vs. 2.8%), and brain metastases (3.2% vs. 0.9%). Conversely, patients with low SIII had higher rates of isolated vault/pelvic recurrence (23.1% vs. 14.3%) and nodal recurrence (16.7% vs. 7.9%). **Conclusion:** Pre-treatment SIII is a simple, cost-effective, and independent prognostic biomarker for survival in advanced epithelial ovarian cancer treated with NACT. It may aid in individual risk stratification and treatment tailoring.

Keywords: Ovarian cancer; Systemic Immune-Inflammation Index; SIII; neoadjuvant chemotherapy; prognosis; survival

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Introduction

Ovarian cancer remains the deadliest gynecologic malignancy worldwide, with most cases presenting in advanced stages (FIGO stage III–IV) [1]. The current standard for patients unfit for primary debulking surgery includes neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) [2]. However, prognosis remains poor despite therapeutic advances, and reliable prognostic markers are needed to guide treatment

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decisions.

The tumor microenvironment and host inflammatory response are increasingly recognized as key modulators of cancer progression [3]. Biomarkers derived from complete blood counts such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and more recently, the Systemic Immune-Inflammation Index (SIII) have shown prognostic significance in various cancers [4–6]. SIII, calculated as (platelet × neutrophil)/ lymphocyte, integrates inflammatory and immune responses and may better reflect the balance between pro-tumorigenic and anti-tumorigenic mechanisms [7].

Neutrophils may promote tumor progression through neutrophil extracellular trap (NET) formation, facilitating metastatic dissemination. Platelets contribute to tumor cell survival via secretion of platelet-derived growth factors and shielding circulating tumor cells from immune recognition. Conversely, lymphopenia reflects impaired anti-tumor immunity. SIII integrates these opposing biological processes into a single composite marker.

While SIII has been validated in gastrointestinal, lung, and hepatocellular cancers, its prognostic utility in ovarian cancer, especially in those receiving NACT, is less understood [8–10]. This study aimed to evaluate the prognostic value of pre-treatment SIII in patients with stage II–IV epithelial ovarian cancer treated with NACT followed by surgery.

Materials and Methods

Study design and patients

This retrospective cohort study included patients diagnosed with FIGO stage II–IV epithelial ovarian carcinoma at Dr B Borooah Cancer Institute from 1 January 2019 to 30 June 2023.

Inclusion criteria

Histologically confirmed epithelial ovarian carcinoma; FIGO stage II–IV disease; received at least 2 cycles of platinum-based NACT; underwent interval debulking surgery or completion surgery; and availability of pre-treatment complete blood count (CBC).

Patients with concurrent infections, autoimmune diseases, or incomplete data were excluded.

Data collection and SIII calculation

Clinical data extracted from electronic medical records. CBC parameters prior to the first cycle of NACT used to calculate SIII as:

SIII = (Platelet count × Neutrophil count) / Lymphocyte count

Receiver operating characteristic (ROC) curve analysis was used to determine the optimal SIII cut-off based on survival outcomes into low group ($\leq 1.22 \times 10^6$) and high group ($> 1.22 \times 10^6$). Receiver operating characteristic (ROC) curve analysis based on overall survival (OS) was performed to determine the optimal SIII cut-off using the Youden Index.

Outcomes

Primary endpoints were overall survival (OS) and progression-free survival (PFS). For patients undergoing interval debulking surgery, OS and PFS were calculated from the date of surgery. For patients who did not undergo surgery, survival was calculated from the date of initiation of neoadjuvant chemotherapy.

Statistical analysis

Kaplan-Meier survival analysis and log-rank test compared OS and PFS between low and high SIII groups. Cox proportional hazards model used for univariate and multivariate analysis. A p-value <0.05 was considered statistically significant and <0.01 was considered very significant. SPSS.v29 used for statistical analysis. All variables entered into multivariate models were selected based on clinical relevance and univariate significance. Complete-case analysis was performed for missing data. The proportional hazards assumption for Cox regression models was assessed using Schoenfeld residuals and was satisfied.

Results

Patient Characteristics

As shown in Table 1, a total of 284 patients met the inclusion criteria. Median age was 52 years (range 26-82). FIGO staging distribution was: Stage II (n=9, 3.2%), Stage III (n=168, 59.2%), and Stage IV (n=107, 37.7%). The histological subtype was predominantly high-grade serous carcinoma (217, 76%).

Out of the 284 patients, 90 patients could not undergo surgery at the end of NACT due to reasons such as inoperability, progressive disease, and poor general condition of the patient.

Optimal cytoreduction was defined as no gross residual disease or residual tumor ≤1 cm. Suboptimal cytoreduction

Table 1. Baseline Demographic Characteristics

Age (in years)	
Mean ± SD	52.33 ± 9.21
Median (Range)	52.00 (26-82)
Age categories [n (%)]	
<40 years	26 (9.2)
40-50 years	84 (29.6)
51-60 years	113 (39.8)
>60 years	61 (21.5)
Menopausal Status [n (%)]	
Premenopausal	102 (35.9)
Postmenopausal	178 (62.7)
Unknown status	4 (1.4)
Parity [n (%)]	
Nulliparous (P0)	24 (8.5)
P1-P2	122 (43.0)
P3-P4	86 (30.3)
P≥5	15 (5.3)

Table 2. Baseline Laboratory Parameters

Parameter	Mean ± SD	Median (Range)
Hemoglobin (g/dL)	10.63 ± 1.54	10.65 (6.0-16.6)
Total leukocyte count (cells/µL)	8492.02 ± 2920.38	8155.00 (1570-27110)
Absolute neutrophil count (cells/µL)	6506.81 ± 2858.49	6190.00 (900-25670)
Lymphocyte count (cells/µL)	1483.09 ± 632.76	1370.00 (390-5180)
Platelet count (cells/µL)	341120.57 ± 151820.08	329500.00 (56000-976000)
NLR	5.34 ± 4.01	4.43 (0.56-32.91)
PLR	277.81 ± 197.70	219.40 (27.34-1303.33)
SIII	$1.88 \times 10^6 \pm 1.9 \times 10^6$	5.87×10^4 to 1.11×10^7

Table 3. ROC Analysis for Calculation of Optimal Cut-off of SIII:

Parameter	AUC	95% CI	p-value	Optimal Cut-off	Sensitivity	Specificity
SIII	0.72	0.66-0.79	<0.001	1225886	68.90%	72.30%

Table 4. Survival Outcomes (PFS and OS) with Respect to SIII: 4A- PFS with Respect to SIII, 4B- OS with Respect to SIII

Parameter	Patients (n)	Median PFS (months)	1-year PFS (%)	2-year PFS (%)	3-year PFS (%)	p-value
SIII (4A)						
$\leq 1.22 \times 10^6$	142 (50.0)	19.7	71.10	33.80	18.30	<0.001
$>1.22 \times 10^6$	142 (50.0)	10.5	37.30	11.30	5.60	
SIII (4B)						
$\leq 1.22 \times 10^6$	142 (50.0)	37.8	91.50	67.60	35.20	<0.001
$>1.22 \times 10^6$	142 (50.0)	21.4	71.80	36.60	18.30	

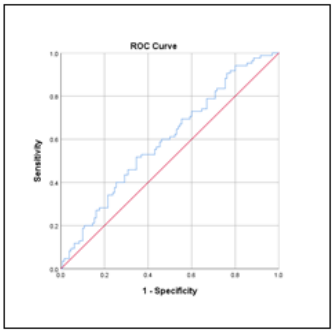


Diagram 1. ROC Analysis for Calculation of Optimal Cut-off of SIII

was defined as residual tumor >1 cm.

Laboratory parameters revealed several noteworthy findings. The mean hemoglobin level was 10.63 ± 1.54 g/dL, indicating mild anemia in the study population. The inflammatory markers showed considerable variability: the mean NLR was 5.34 ± 4.01 (median 4.43), with a wide range (0.56-32.91), and the mean PLR was 277.81 ± 197.70 (median 219.40), also with substantial variability (range 27.34-1303.33). Systemic Immune-Inflammation Index (SII) showed the highest variability among inflammatory markers, with a mean of $1.88 \times 10^6 \pm 1.9 \times 10^6$ and median of 1.22×10^6, ranging from 5.87×10^4 to 1.11×10^7. These elevated inflammatory markers are consistent with the systemic inflammatory response often observed in advanced malignancy. The wide ranges in these values suggest significant heterogeneity in the inflammatory status among patients, which may have prognostic implications (Table 2).

ROC curve analysis

The optimal cut-off values were 1225886 for SIII (sensitivity 68.9%, specificity 72.3%). Patients were categorized into low SIII [cut-off value $\leq 1.22 \times 10^6$, (n=142)] and high SIII [cut-off value $> 1.22 \times 10^6$, (n=142)] groups (Table 3) (Diagram 1).

Survival Outcomes

With the median follow up period of 41 months, median PFS for low SIII group and high SIII groups were 19.7 months and 10.5 months (p<0.001), respectively. Median OS for low SIII group and high SIII groups were 37.8 months and 21.4 months (p<0.001), respectively (Diagram 2 and 3).

On multivariate analysis, after adjusting for age, FIGO stage, and residual disease post-IDS, high SIII remained an independent predictor of poor PFS (HR 2.03; 95% CI 1.36-3.04; p< 0.001). High SIII also independently predicted for worse OS (HR 2.42; 95% CI 1.52-3.85; p<0.01) (Diagram 4 and 5).

The correlation between SIII values and site of progression revealed statistically significant differences (p=0.004). Patients with high SIII more frequently experienced progression at multiple sites (27.8% vs. 16.7%) and had higher rates of progression involving ascites (10.3% vs. 4.6%), pleural/lung metastases (7.1% vs. 2.8%), and brain metastases (3.2% vs. 0.9%) compared

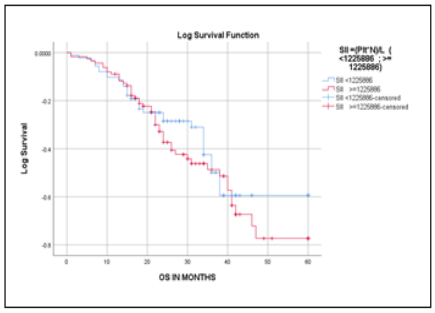


Diagram 2. Kaplan Meier Analysis for Progression Free Survival

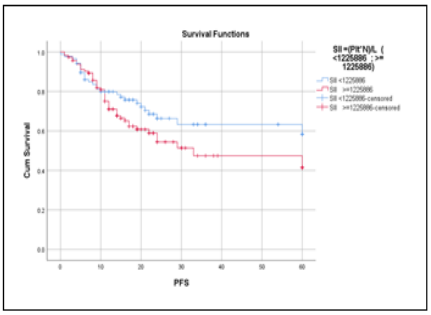


Diagram 3. Kaplan Meier Analysis for Overall Survival

to those with lower SIII values. Conversely, patients with low SIII had higher rates of isolated vault/pelvic recurrence (23.1% vs. 14.3%) and nodal recurrence (16.7% vs. 7.9%). Peritoneal/omental recurrence [(14 % (low SIII) vs. 13 % (high SIII)] and liver metastases [8 % (low SIII) vs. 11 % (high SIII)] were similar amongst the groups (Table 4 and 5).

These findings suggest that high SIII may be associated with more widespread metastatic disease and a higher propensity for distant metastases, particularly to sites like the pleura /lungs and brain. The higher rate of multiple-site recurrence in patients with high SIII could reflect more aggressive tumor biology and greater propensity for hematogenous spread, potentially mediated by heightened systemic inflammation. Although individual site comparisons were not adjusted for multiple testing, the overall distribution difference was statistically significant (p=0.004) (Table 6, 7) (Diagram 6 and 7).

These findings suggest that high SIII may be associated with more widespread metastatic disease and a higher propensity for distant metastases, particularly to sites like the pleura /lungs and brain. The higher rate of multiple-site recurrence in patients with high SIII could reflect more aggressive tumor biology and greater propensity for hematogenous spread, potentially mediated by heightened systemic inflammation.

Discussion

Our study demonstrates that high pre-treatment SIII is significantly associated with poorer PFS and OS in patients with stage II–IV ovarian cancer treated with NACT. SIII integrates three major immune-inflammatory parameters and may serve as a better prognostic indicator than NLR (Neutrophil Lymphocyte Ratio) or PLR (Platelet Lymphocyte Ratio) alone [6, 7]. This finding is consistent with previous studies in other cancers, including hepatocellular [8], gastric [9], and lung carcinomas [10], where elevated SIII predicted inferior outcomes.

In ovarian cancer, inflammation promotes tumor growth, angiogenesis, and resistance to therapy [11]. Elevated neutrophils suppress cytotoxic lymphocytes, platelets shield tumor cells from immune attack, and lymphopenia reflects reduced anti-tumor immunity [12].

High pre-treatment SIII may reflect aggressive tumor biology with higher likelihood of suboptimal cytoreduction. Incorporating SIII into pre-operative evaluation may help refine surgical expectations and inform multidisciplinary decision-making.

Patients with markedly elevated SIII may represent a subgroup with higher propensity for distant metastatic

Table 5. Multivariate Analysis for Progression-Free Survival including SIII

Variable	HR	95% CI	p-value
Age >60 years	1.49	1.02-2.18	0.042
FIGO Stage IV	1.78	1.23-2.57	0.002
SIII >1.22 x 10^6	2.03	1.36-3.04	<0.001
Grade 3	1.39	0.78-2.47	0.265
Suboptimal cytoreduction	1.89	1.26-2.83	0.002
No surgery	2.31	1.56-3.42	<0.001

Table 6. Multivariate Analysis for Overall Survival Including SIII

Variable	HR	95% CI	p-value
Age >60 years	1.76	1.12-2.77	0.014
FIGO Stage IV	2.05	1.33-3.16	0.001
SIII >1.22 x 10^6	2.42	1.52-3.85	<0.001
Grade 3	1.57	0.79-3.14	0.202
Suboptimal cytoreduction	2.24	1.39-3.60	0.001
No surgery	3.08	1.97-4.82	<0.001

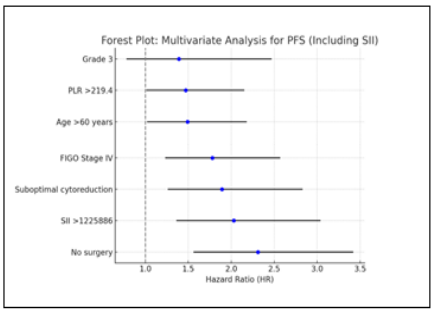


Diagram 4. Forest Plot Depicting Multivariate Analysis for Progression Free Survival Including SIII

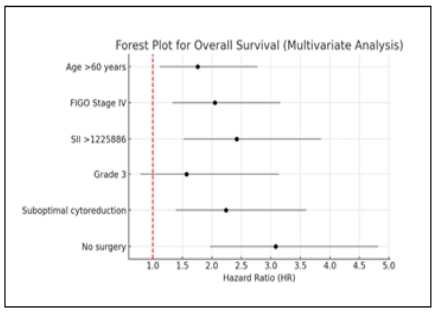


Diagram 5. Forest Plot Depicting Multivariate Analysis for Overall Survival Including SIII

dissemination. Future studies may evaluate whether such patients benefit from more comprehensive staging imaging, including brain MRI in selected cases.

Our findings suggest that high SIII may be associated with more widespread metastatic disease and a higher propensity for distant metastases, and are associated with poorer survival outcomes. The higher rate of multiple-site recurrence in patients with high SIII could reflect more aggressive tumor biology and greater propensity for hematogenous spread, potentially mediated by heightened systemic inflammation. The higher rates of

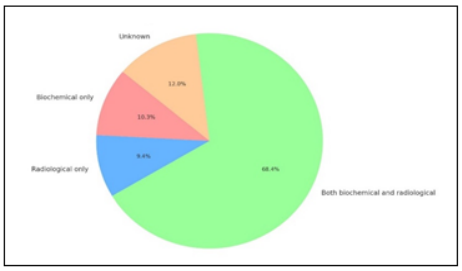


Diagram 6. Pattern of Recurrence/ progression

isolated vault/pelvic and nodal recurrence in the low SIII group may suggest a more locoregional disease pattern, potentially amenable to secondary cytoreduction or targeted radiotherapy strategies.

High-SIII patients may represent candidates for intensified first-line maintenance strategies, including PARP inhibitor-based combinations or bevacizumab-containing regimens, and prioritization for clinical trials exploring therapies targeting inflammatory pathways.

Our results suggests incorporating SIII into pre-treatment assessments to stratify patients with advanced epithelial ovarian cancer by prognostic groups. This observation supports the potential utility of SIII not only in predicting the likelihood of progression but also in anticipating the pattern and extent of recurrence, which may have implications for surveillance strategies, consideration for clinical trials or alternative treatment strategies, and post-recurrence management. However, further validation in prospective studies is required.

Retrospective single-center analysis, and lack of serial SIII measurements during treatment are few of the limitations of the study. Potential residual confounding cannot be excluded. Serial SIII measurements were not available. External validation in independent cohorts is warranted.

In conclusion, systemic immune inflammation index

Table 6. Correlation between SIII values and site of progression

Recurrence Pattern	Low SIII ≤1.22 x 10^6 (%)	High SIII >1.22 x 10^6 (%)	p-value
Biochemical only	15 (13.9)	9 (7.1)	0.013
Radiological only	13 (12.0)	9 (7.1)	
Both biochemical and radiological	65 (60.2)	95 (75.4)	
Unknown	15 (13.9)	13 (10.3)	

Table 7. Pattern of Recurrence with Respect to SIII

Site of Progression	Low SIII ≤1.22 x 10^6 (%)	High SIII >1.22 x 10^6 (%)	p-value
Vault/Pelvic	25 (23.1)	18 (14.3)	0.004
Nodal	18 (16.7)	10 (7.9)	
Peritoneal/Omental	14 (13.0)	13 (10.3)	
Liver	8 (7.4)	11 (8.7)	
Ascites	5 (4.6)	13 (10.3)	
Pleural/Lung	3 (2.8)	9 (7.1)	
Brain	1 (0.9)	4 (3.2)	
Multiple sites	18 (16.7)	35 (27.8)	
Other sites/Unknown	16 (14.8)	13 (10.3)	

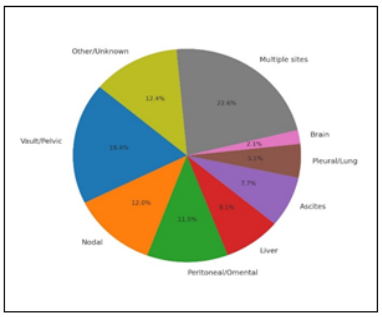


Diagram 7. Sites of Recurrence/progression

(SIII) is a promising, cost-effective, and independent prognostic marker in advanced epithelial ovarian cancer treated with neoadjuvant chemotherapy. It could help refine risk stratification and personalize treatment in resource-constrained settings.

Abbreviations

AUC: Area Under the Curve, CBC: Complete Blood Count, CI: Confidence Interval, FIGO: International Federation of Gynecology and Obstetrics, HR: Hazard Ratio, IDS: Interval Debulking Surgery, NACT: Neoadjuvant Chemotherapy, NLR: Neutrophil-to-Lymphocyte Ratio, OS: Overall Survival, PFS: Progression-Free Survival, PLR: Platelet-to-Lymphocyte Ratio, ROC: Receiver Operating Characteristic, SD: Standard Deviation, SIII: Systemic Immune-Inflammation Index.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Committee of Dr B Borooah Cancer Institute. Due to the retrospective nature of the study, the requirement for informed consent was waived. All procedures performed were in accordance with institutional and national ethical standards. Ethical clearance certificate number.-BBCI-TMC/Misc-01/MEC/398/2024.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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No specific funding was received for this study.

Authors' contributions

PSR and KM conceptualized the study. KM contributed to data collection. KM performed the statistical analysis. PSR and KM drafted the manuscript. PSR and DB supervised the manuscript finalization process. All authors contributed to manuscript revision, read, and approved the final version.

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