ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 10 | October - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

STUDY OF CHANGE IN SYSTEMIC IMMUNE-INFLAMMATION INDEX AS A RESPONSE PREDICTOR IN GASTROESOPHAGEAL JUNCTION CANCER POST NEOADJUVANT CHEMOTHERAPY

Oncology

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ABSTRACT

Introduction: This study analyses the prognostic significance of change in systemic immune-inflammation index (ΔSII) as a predictor of pathological response to neoadjuvant chemotherapy in gastroesophageal junction adenocarcinoma patients. **Objective:** To study the correlation between ΔSII, tumour response grade, clinicopathological parameters in gastroesophageal junction cancer patients post NACT. **Materials And Methods:** This prospective observational study enrolled 46 patients with gastroesophageal junction adenocarcinoma receiving neoadjuvant chemotherapy at a tertiary cancer centre. Systemic immune-inflammation index (SII) values were calculated before and after chemotherapy, with ΔSII defined by subtracting the pre-NACT value from post-NACT value. Tumor regression grade (TRG) was assessed using standardized pathological criteria. Statistical analysis included receiver operating characteristic (ROC) curve analysis and chi-square tests to evaluate associations between ΔSII and clinicopathological parameters. **Results:** The median age of the cohort was 59.5 years, with 63.04% male patients while 36.95% were female patients. Majority of the patients had tobacco exposure. 43.48% patients had response to chemotherapy (TRG 0-2). Pre-NACT SII had good predictive value for response but Post-NACT SII and ΔSII demonstrated limited predictive value. Notably, ΔSII < 0 was significantly associated with favorable tumor regression grade (TRG 0-2: 75.0% vs. TRG 3: 3.8%, p = 0.001) and other variables like LVI, PNI, margins, gender, stage, her 2 had no significant association with ΔSII < 0. **Conclusion:** ΔSII represents a readily available and cost-effective biomarker for predicting pathological response to neoadjuvant chemotherapy in gastroesophageal junction cancer. Patients with decreased SII following treatment demonstrate significantly better pathological response rates, suggesting potential utility for treatment optimization and prognostic stratification.

KEYWORDS

gastroesophageal junction cancer, systemic immune-inflammation index, neoadjuvant chemotherapy, tumor regression grade, biomarker.

INTRODUCTION:

Gastroesophageal junction cancer are amongst the most challenging and aggressive cancers [1]. Neoadjuvant chemotherapy followed by surgery is the standard treatment for locally advanced gastroesophageal junction cancer, but predicting response remains a challenge [2]. Perioperative chemotherapy, including neoadjuvant chemotherapy aims to improve survival rates by downstaging the tumor and eradicating micro metastases [3]. Assessing response to chemotherapy remains a challenge but with better understanding of cancer biology treatment of this challenging malignancy can be understood better.

Inflammation acts as fertile ground for cancer progression, proliferation, invasion, migration and reducing response to therapeutic agents [4]. Systemic inflammation is a dynamic process based on balance between host immune and inflammatory responses and monitoring of systemic inflammation could offer a minimally invasive approach for assessing response to neoadjuvant chemotherapy and this could help in prognosis of gastroesophageal junction cancer undergoing neoadjuvant chemotherapy [5,6].

The pretreatment SII has been shown to be of prognostic significance in gastroesophageal cancer patients receiving NACT [7].The association between SII changes and pathological tumor regression grade has not been studied extensively in GEJ cancer patients receiving NACT. Inflammation is a dynamic process that changes with treatment, hence ΔSII in patients receiving neoadjuvant chemotherapy as a part of response predictor to chemotherapy can help understand the tumor behavior. Previous research on gastric and gastroesophageal cancer only looked at inflammation levels before treatment started, missing the complete picture of how patients respond to chemotherapy. This study is one of the few studies to track inflammation changes throughout treatment. This approach would help in timely adjustment of treatment strategies , potentially improving patient outcome and refining approaches to this challenging malignancy.

MATERIALS AND METHODS:

The current study is a prospective observational study conducted from February 2024 to July 2025 at a tertiary cancer institute. Data was procured from patients following up in Medical oncology OPD and those admitted in IPD.

Patient Selection:

Inclusion Criteria:

1. Curative surgery for the disease after NACT.
2. TRG reported in pathological examination.
3. Complete clinical and laboratory data.
4. Written informed consent.

Exclusion Criteria:

1. Patients with inflammatory and autoimmune disease.
2. Patients with complication such as bleeding, infection.
3. Denied consent.

Demographic, pathological, clinical data, date of diagnosis, NACT regimen were taken from patient records. Clinical staging was conducted using either contrast.enhanced chest and abdominal CT or PET/CT, while both the clinical (c) and post-NACT pathological (yp) stages were assigned according to the AJCC 8th-edition TNM system (2017).

Pathologist evaluated the surgical specimen. Modified Ryan classification system adapted by the College of American Pathologist (CAP) was used for assessment of response to NACT. This classification has categorised TRG into 4 tiers depending on the relative proportion of residual tumor and stromal fibrosis. TRG 0, 1 and 2 were taken as responders to NACT while TRG 3 was taken as non-responders to NACT (table 1).

Table 1 : Modified Ryan Classification For Tumour Regression Grading System [8]

Description	Tumour Regression Grade
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near complete response)	1
Residual cancer with evident tumour regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumour regression (poor or no response)	3

Laboratory data mainly complete blood count (CBC) was done before starting NACT and 14 days after the last NACT cycle prior to surgery. Data was obtained from patient records as this was done routinely. SII was calculated as (neutrophil count × platelet count)/lymphocyte count. Change in SII (ΔSII) was calculated by subtracting the pre-NACT value from post-NACT value. Categorization of patients was done into two groups i.e. ΔSII>0 and ΔSII<0.

Primary Outcome: Pathological response of gastroesophageal junction cancer to NACT measured as TRG (0-2) versus TRG 3.

Secondary Outcome: Association of ΔSII with other clinicopathologic parameters such as gender, LVI, PNI, margins, her 2,stage.

Statistical Analysis:
Statistical analysis was done by employing SPSS (Statistical Package for the Social Sciences), version 23. After entering data into Microsoft Excel, it was imported into SPSS for further analysis. Descriptive statistics were evaluated for all variables that were analysed. Quantitative variables were evaluated by employing mean or median values, and standard deviation (SD) or interquartile range (IQR). When dealing with qualitative variables, frequencies and proportions were determined.

Categorical variables were determined for associations by performing a Chi-square test and when observed value is less than 5 in a cell, fisher's exact test was used . Area under ROC curve was calculated for estimating optimum cut-off values for SII pre-NACT,SII post-NACT and ΔSII sensitivity as well as specificity concerning gastroesophageal junction cancer outcomes.

Ethical Approval And Consent To Participate: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Medical ethics committee issued approval KMIO/MEC/2024/02/PG/MO/20. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

RESULTS:

Patient Characteristics And Blood Parameters:
A total of 46 patients diagnosed with gastroesophageal carcinoma were included in this study, 63.04% (n=29) were males while 36.95% (n=17) were females. The median age of diagnosis was 59.5 years. Following the diagnosis of gastroesophageal junction carcinoma, the mean hemoglobin level was 13.2 gm/dl, mean total leucocyte count was 6160/microL, mean absolute neutrophil count was 3640/microL, mean lymphocyte count was 1960/microL and mean platelet count was 220000/microL. Abdominal pain (54.30%)was the most common presenting symptom followed by dysphagia (47.82%), vomiting (10.86%), fatigue (6.52%) and loss of appetite (6.52%).

Surgical Approaches:
All the patient of the cohort had adenocarcinoma histology . 91.30% (n=43) of patients belonged to stage III and IVA while 8.70% (n=3) had stage I and II. Patients were posted for surgery post completion of NACT of which 30.43% (n=14) underwent trans-hiatal esophagectomy and 69.56% (n=32) underwent total gastrectomy.

Addiction History:
Table 2: Type Of Addiction Amongst Patients With Addiction History.

Addiction	Prevalence
Smoking	21.74%
Tobacco chewer	17.39%
Alcoholic	6.52%
Smoker and alcoholic	21.74%
No addiction	32.61

67.39% (n=31) disclosed addiction history while 32.61% (n=15) did not reveal any history of addiction. Amongst the patient who revealed addiction history ,21.74% (n=10) had history of smoking, 17.39% (n=8) had history of tobacco chewer, 6.52% (n=3) had history of alcohol consumption and 21.74% (n=10) had history of smoking and alcohol consumption both (table 2).

Predictors Of Response And Tumor Regression Grade:

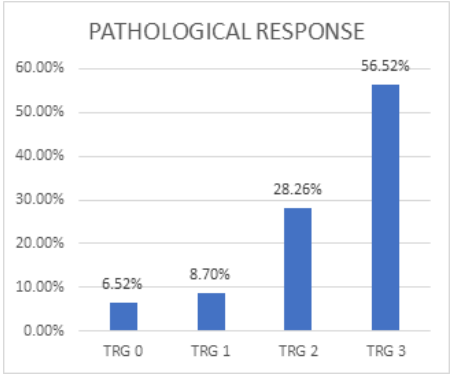

Figure 1: Tumour regression grade (TRG) distribution for the cohort.

6.52% (n=3) patients had complete pathological response, 8.70% (n=4) patients had near complete response, 28.26% (n=13) patients had partial response while 56.52%(n=26) patients had no response to chemotherapy. Of the total patients 86.96% (n=40) received FLOT regimen as NACT while remaining 13.04% (n=6) received mFOLFOX as NACT, median cycles of NACT received was four in the cohort (figure 1).

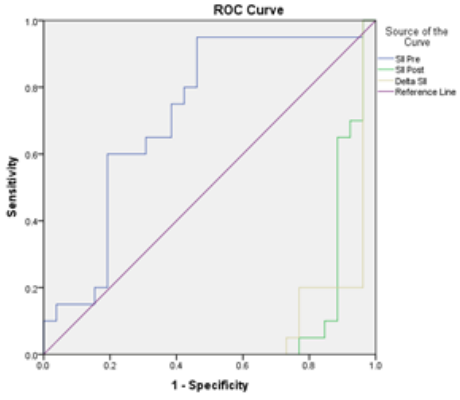

Figure 2: ROC curve comparing SII (pre-NACT), SII (post-NACT), and ΔSII against the reference diagonal.

ROC curve analysis revealed significant differences in the predictive ability of the three SII metrics evaluated. Pre-treatment SII demonstrated fair predictive ability with an AUC of 0.721 (95% CI: 0.569-0.873, p = 0.011), indicating performance significantly better

than chance. The optimal cutoff value for pre-treatment SII was 351.91, yielding a sensitivity of 95.0% and specificity of 53.8%. In contrast, post-treatment SII and ΔSII both exhibited poor discriminatory power. Post-treatment SII had an AUC of 0.098 (95% CI: 0.000-0.199, $p < 0.001$), while ΔSII achieved an AUC of 0.079 (95% CI: 0.000-0.165, $p < 0.001$). Despite statistical significance, these extremely low AUC values indicate that neither post-treatment SII nor ΔSII possess meaningful predictive ability when analyzed as continuous variables (figure 2).

Table 3: Association Of Delta SII (ΔSII) And Clinical Variable.

		Dental SII		Total	p-value
		DELTA SII <0	DELTA SII>0		
Gender	Female	5	12	17	0.399
		29.4%	70.6%	100.0%	
	Male	11	18	29	
		37.9%	62.1%	100.0%	
LVI	Negative	10	26	36	0.244
		27.78%	72.22%	100.0%	
	Positive	1	9	10	
		10%	90%	100.0%	
PNI	Negative	12	21	33	0.719
		36.36%	63.63%	100.0%	
	Positive	4	9	13	
		30.77%	69.23%	100.0%	
Margins	Negative	15	28	43	0.726
		34.9%	65.1%	100.0%	
	Positive	1	2	3	
		33.3%	66.7%	100.0%	
HER2	Negative	15	30	45	0.348
		33.3%	66.7%	100.0%	
	Positive	1	0	1	
		100.0%	0.0%	100.0%	
STAGE	I-II	2	2	4	0.60
		50%	50%	100%	
	III-IVA	14	28	42	
		33.33%	66.66%	100%	
TRG Response	0-2	15	5	20	0.001
		75%	25%	100.0%	
	3	1	25	26	
		3.8%	96.2%	100.0%	
Total		16	30	46	
		34.8%	65.2%	100.0%	

Among the total patients with good response to chemotherapy (TRG 0-2), 75% (n=15) patients had ΔSII <0 while 25% (n=5) patients had ΔSII >0. Patients with poor response to chemotherapy (TRG 3) had ΔSII <0 in 3.8% (n=1) of patients and ΔSII >0 in 96.2% (n=25) patients. The association was statistically significant (p=0.001) suggesting it to be a good predictor of response.

ΔSII status didn't demonstrated significant associations with other pathological parameters. Lymph vascular invasion did not show a relationship with ΔSII status ($p = 0.244$). Among patients with negative LVI, 27.78% had $\Delta SII < 0$ compared to 72.22% with $\Delta SII \geq 0$. However, among patients with positive LVI, only 10% demonstrated $\Delta SII < 0$, while 90% had $\Delta SII \geq 0$.

A similar finding was observed for perineural invasion ($p = 0.719$), with patients having negative PNI showing 36.36% $\Delta SII < 0$ versus 63.63% $\Delta SII \geq 0$, while those with positive PNI demonstrated 30.77% $\Delta SII < 0$ versus 69.23% $\Delta SII \geq 0$. There was no statistically significant relation between PNI and ΔSII. No significant associations were observed between ΔSII status and clinical stage (p=0.60), gender ($p = 0.399$), surgical margin status ($p = 0.726$), or HER2 status ($p = 0.348$) (table 3).

DISCUSSION:

The current study aimed to analyse the association of systemic immune inflammation index and its dynamic changes in patients of gastroesophageal junction cancers receiving neoadjuvant chemotherapy as an inexpensive, novel marker of response to chemotherapy correlating with the pathological response.

In our study the median age of diagnosis was 59.5 years and male sex had a greater prevalence compared to female, similar observation were made in a study by Goense et al.[9]. In our cohort 67.39% patients disclosed addiction history while 32.61% patients did not disclose any addiction history. Majority of patients in the cohort with addiction history had exposure to tobacco in the form of smoking or chewing tobacco this finding is in congruence with the available literature suggesting link between smoking as a risk factor for gastroesophageal junction carcinoma [10,11]. Alcoholism is not clearly associated with the risk of gastroesophageal adenocarcinoma [11], in our cohort 28.26% patients had history of alcohol consumption but the majority of study population also had history of tobacco exposure which would have been a confounding factor.

In our cohort, 6.52% (n=3) patients had TRG 0, 8.70% (n=4) patients had TRG 1, 28.26% (n=13) patients had TRG 2 while 56.52%(n=26) patients had TRG 3. Concluding that combined total and subtotal regression (TRG 0 and TRG 1) was 15.21% while 28.26% (TRG 3) had partial regression which is similar to the data for patients of gastroesophageal junction cancer post platinum based preoperative chemotherapy [12,13].

Systemic Immune Inflammation Index And Predictor Of Pathological Response:

The study revealed Pre-NACT SII value of 351.91 had a good predictive value for pathological response with a sensitivity of 95% and specificity of 53.80%. The value of pretreatment SII has been proved in gastric and other cancers also and has been found to be a good predictor of pathological response [14]. The post-NACT SII and the ΔSII were below the reference line in ROC curve which suggest it to be a poor determinant of pathological response. For a cut-off value of 265.19 for post-NACT SII and -243.54 for ΔSII it has good sensitivity but poor specificity, implying is to be a good screening test but due low specificity value a confirmatory test is required.

Our study depicted that change in systemic immune inflammation index (ΔSII) when stratified into two groups of ΔSII <0 and ΔSII >0 showed meaningful associations with the clinical variables. A ΔSII <0 was associated with good pathological response (TRG 0-2) to NACT compared to when ΔSII >0 (p=0.001), similar finding was observed in a study by Demircan et al.[15]. The biological rationale for these findings lies in the complex interplay between systemic inflammation and cancer progression. Neoadjuvant chemotherapy not only directly targets cancer cells but also modulates the inflammatory microenvironment. Assessment of positive LVI in the pathological specimen didn't correlate with ΔSII status <0 (p=0.244), also a positive PNI failed to show a significance in patients with ΔSII <0 (p=0.719), these findings are similar to the other similar study where LVI and PNI were found to be an independent prognostic factor [15,16]. The other variable like her 2 neu, stage, margin, gender had no significant association similarly seen in a separate study [15]. This finding substantiate ΔSII <0 to be an independent prognostic marker predicting response to neoadjuvant chemotherapy in gastroesophageal junction cancer.

Limitations And Future Directions:

Several limitations must be acknowledged in interpreting these results. The modest sample size limits the generalizability of findings and precludes detailed subgroup analyses. The single centre design may introduce bias and validation in multicentre cohorts is essential before implementation.

CONCLUSION:

This shows systemic immune inflammation index (SII) and ΔSII <0 to be a good predictor of response to neoadjuvant chemotherapy in gastroesophageal junction cancer. This SII and ΔSII <0 could be used as an affordable, non-invasive and easily accessible marker to access response and tailor therapy of patients and also improve surveillance.

Declarations

Consent For Publication: Written informed consent obtained.

Availability Of Data And Material - The datasets generated and/or analyzed during the current study are not publicly available due to privacy of the study participant.

Conflicts Of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Funding: This study has not received any funding.

Acknowledgement: Residents and faculty of medical oncology and

other supporting departments.

Abbreviations:
SII : Systemic immune inflammation index.
TRG: Tumor Regression grade
NACT: Neo-adjuvant chemotherapy
GEJ: Gastroesophageal junction
LVI: Lymphovascular invasion
PNI: Perineural invasion
ΔSII: Change in systemic immune inflammation index

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