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Original Article

Pathology Section

Significance of Systemic Inflammation and Inflammation Response Index in Oral Squamous Cell Carcinoma: A Cross-sectional Study

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ABSTRACT

Introduction: Among novel markers, the most recently developed are the Systemic Immune-Inflammation Index (SII) and Systemic Inflammation Response Index (SIRI). SII and SIRI are composite inflammatory indices derived from different blood cell populations: SII incorporates platelets, neutrophils, and lymphocytes, while SIRI incorporates neutrophils, monocytes, and lymphocytes , and were shown to be independent predictors of overall survival in patients with lung, breast, oesophageal and urologic cancers. The objective was to determine the utility of common inflammatory markers such as SII and SIRI in Oral Squamous Cell Carcinoma (OSCC).

Aim: To establish role of SII and SIRI in OSCC and its significance as prognostic marker in OSCC taking into consideration of grade and stage of disease.

Materials and Methods: The current cross-sectional analytical study was conducted in a tertiary health centre, R L Jalappa Hospital, Department of Pathology at Devaraj Urs Medical College, Tamaka, Karnataka, India utilising case files of OSCC patients received between January 2023 and December 2023 with data included from same period of time to estimate the SII and SIRI in OSCC and its association with grade and stage of disease. The data was compiled and results were analysed using Microsoft Statistical Package for the Social Sciences (SPSS) software 2022 after entering all the data on a spread sheet in October 2024. Descriptive statistics and Fisher's exact test were applied as appropriate.

Results: With age group of 30 years to 90 years, with a mean age group of 60 years± comprising males 33 (66%) and females 17(34%). The SII showed statistically significant association with grade (p=0.0013), of OSCC. The association of SII with stage (p=0.586) and SIRI with grade (p=1.001) and stage (p=0.79) respectively did not show statistically significant association. Majority of OSCC showed high SII and SIRI values.

Conclusion: The SII and SIRI as prognostic markers have not been established in OSCC. Although SII has shown a significance with grade of disease in the present study which can be used as a prognostic marker and outcome of the disease. But its significance with stage of disease was not stabilised. On other hand SIRI showed no significance with either grade or stage of the disease. Minimal cut-off value of SII and SIRI also needs to be validated so both parameters can be used as prognostic factors in OSCC.

Keywords: Head and neck cancer, Inflammatory biomarkers, Systemic Immune-Inflammation Index, Systemic Inflammation Response Index

INTRODUCTION

The OSCC is a squamous-differentiated cancer that develops in the oral cavity and tongue mucosa. Oral cancer, accounts for around 3.5 million new cases and 1.7 million deaths worldwide each year [1]. Of all cancers, oral cancer makes up 2.0% [1]. The incidence rate is especially rising sharply in the age group of fourth decade [1]. The International Agency for Research on Cancer (IARC) has released data showing that it is the seventh most prevalent malignant neoplasm in men worldwide [2]. Factors such as smoking, alcohol consumption, lifestyle changes and early detection may contribute to the rise in cases.

Oral cancer has a survival rate of about 50%. Advancements in traditional treatment modalities, i.e., surgery, chemotherapy, and radiotherapy, have not been able to noticeably increase the survival rate, yet the side-effects of these treatments are significant [1]. It is possible to better understand the biological behaviour of the tumour and the natural history of the disease when the factors influencing outcome are known. In order to improve risk classification for adjuvant therapy modalities or more aggressive treatment in patients with distant metastases, numerous new biomarkers have been studied [2].

Changes in the systemic inflammatory response to tumour cells, especially white blood cells and platelets, have drawn attention as valuable prognostic biomarkers. Among novel markers, the most recently developed are the SII and SIRI. They are derived from three types of inflammatory cells (lymphocytes, neutrophils and monocytes) and were shown to be independent predictors of overall survival in patients with lung, breast, oesophageal and urologic cancers. High preoperative SII and SIRI were also shown to be independent prognostic factors in patients with OSCC, but the data are still very limited [1].

A high SII has been found to be a strong predictor of long-term survival in a variety of malignant tumours and has been linked to advanced clinico-pathological features. The systemic inflammatory response linked to cancer has emerged as a key predictor of tumour advancement. The degree of systemic inflammation is then reflected by biomarkers that develop, leading to a variety of circulating blood cell count-based inflammatory indicators that, when combined with the Tumour-Node Metastasis (TNM) system in various cancers, have improved prognosis prediction. For OSCC patient clinical treatment and prognosis prediction, SII may prove to be a valuable and meaningful biomarker. A reliable predictor of tumour differentiation is SII. Changes in the systemic inflammatory response to tumour cells, especially white blood cells and platelets, have drawn attention as valuable prognostic biomarkers [1]. The

aim of the present study was to find significance between SII and SIRI with grade and stage of disease.

MATERIALS AND METHODS

The present study is a cross-sectional analytical study was conducted in a tertiary health centre, R L Jalappa Hospital, Department of Pathology at Devaraj Urs Medical College, Tamaka, Kolar, Karnataka, India utilising case files of OSCC received between January 2023 and December 2023 as the source of data and was analysed in October 2024. Following ethical clearance from the central ethics committee (IEC number- SDUAHER/KLR/R&D/CEC/S/PG/32/2024-25) and informed consent from patient were taken. The grade and stage of the disease were noted. The grading were given as well-differentiated, moderately differentiated and poorly differentiated and staging was given from Stage I to IV, both according to World Health Organisation (WHO) classification of head and neck 2022/2024 and AJCC 8th edition 2017 for tumour classification. A total of 50 subjects were considered by using Burderer, NMF (1996) of different age groups, both male and female [3].

Inclusion criteria: Newly diagnosed cases of OSCC confirmed by histopathology were included.

Exclusion criteria: Post-chemotherapy, Post-radiotherapy cases, Postsurgery cases, recurrent cases or any other cancer in the patient.

Study Procedure

Pre-operative complete blood count of freshly diagnosed cases whose Complete Blood Count (CBC) before the surgical procedure during the pre-anaesthetic check-up and confirmed by histopathology were considered for the study. Clinicopathological data with grade and stage of disease was collected from case files. Data on complete blood counts was collected from haematology section analyser to calculate the SII and SIRI for each patient**.** The mean age of patient, grade and stage of the disease and data like platelet count, absolute neutrophil count and absolute lymphocyte count for SII, collected and for SIRI absolute neutrophil, absolute monocytes and absolute lymphocytes. SII was calculated using the formula SII=(Platelet count×Absolute neutrophil count)/Absolute lymphocyte count where P, N, and L represent the platelet count, absolute neutrophil count, and absolute lymphocyte count, respectively. SIRI=(Absolute neutrophil count×Absolute monocyte count)/Absolute lymphocyte count were N, M and L represent absolute neutrophil count, absolute monocyte count and absolute lymphocyte count respectively. Information required for the study was collected from case files and from laboratory of RL Jalappa Hospital. Statistical analysis was performed to determine the association between SII and SIRI with grade and stage of the disease.

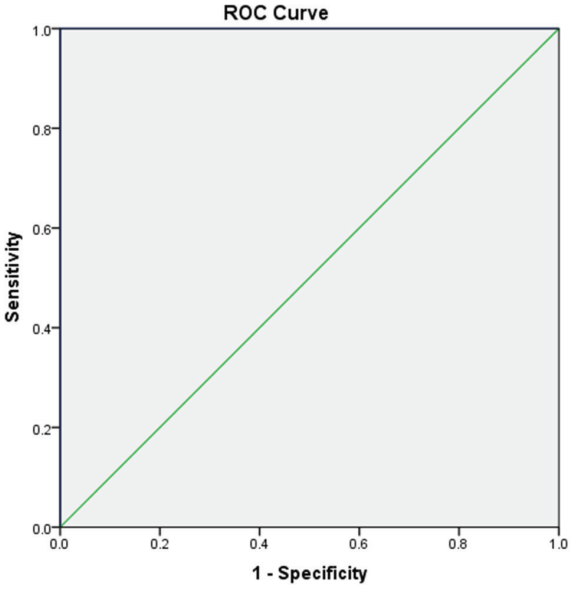
STATISTICAL ANALYSIS

Statistical data was entered in Microsoft excel sheet and analysed by SPSS software version 2022. Descriptive statistics and Fisher's exact tests were applied as appropriate. Receiver Operating Characteristic (ROC) analysis was done to derive the cut-off values for SII and SIRI. Based on cut-off value the cases were divided as high and low SII and SIRI, respectively. A minimum level of statistical significance was considered at p level of <0.05.

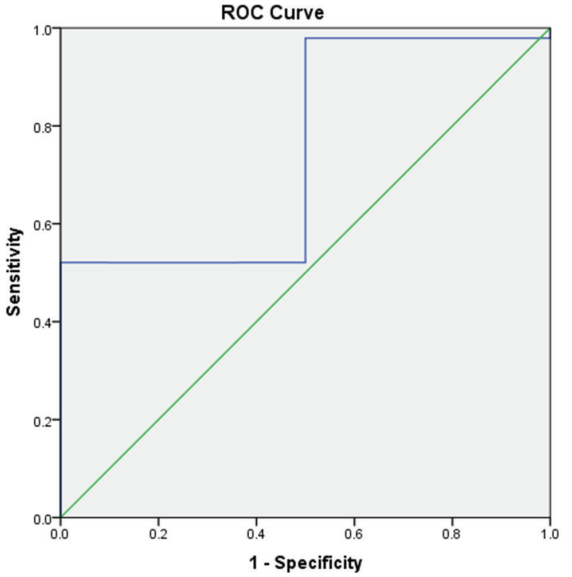
RESULTS

A total of 50 study subjects were enrolled in the study. The cases included were from the age group of 30 years to 90 years, with a mean age group of 60 years±12.71 years. Male were 33 (66%) and female were 17(34%). Out of 50 subjects 34 subjects (68%) were well-differentiated, 14 subjects (28%) were moderately differentiated, and 2 subjects (4%) were poorly differentiated. Out of 50 cases 2 subjects (4%) were in Stage-I, 10 subjects (20%) were in Stage-II, 17 subjects (34%) were in Stage-III and 21 subjects (42%) in Stage-IV,

The ROC analysis showed the cut-off for SII as 581 for 98% sensitivity and 100% specificity Area Under the Curve (AUC)=1 with confidence interval of 95% [Table/Fig-1]. SIRI ROC analysis showed cut-off of 0.910 for 96% sensitivity and 50% specificity (AUC=0.750) with confidence interval of 95%. Though no particular cutoff is available, this ROC shows more sensitivity of SIRI which can be used in prognostication of OSCC cases [Table/Fig-2].



[Table/Fig-1]: ROC analysis showing the cut-off for SII as 581 for 98% sensitivity and 100% specificity (CI=95%, AUC=1).



[Table/Fig-2]: ROC analysis showing cut off of SIRI, 0.910 for 96% sensitivity and 50% specificity (CI= 95%, AUC=0.750).

The SII was significantly associated with tumour grade, with a p-value of 0.0013 [Table/Fig-3]. High SII values were observed as the tumour becomes less differentiated. A 94.2% of well-differentiated tumour had high SII. A 85.7% of moderately differentiated tumour had high SII and 100% of poorly differentiated tumours had high SII.

High SII (>581) was present in the vast majority (92%) of cases, across all tumour stages [Table/Fig-4]. Even in early-stage disease (Stage I and II), high SII was found in 100% and 80%, respectively. In advanced stages (Stage III and IV), high SII was even more prevalent (94.1% and 95.2%). Low SII (<581) was seen only in a small percentage: 20% in Stage II, 5.8% in Stage III, and 4.7% in Stage IV. Stage I had no low SII cases. Although a high SII appears more common in advanced stages, the association between SII and tumour stage in OSCC was not statistically significant (p=0.586) in this study.

Grade	Low SII (<581)	High SII (>581)	Total cases	p-value
Well-differentiated	2 (5.8%)	32 (94.2%)	34 (68%)	0.0013
Moderately differentiated	2 (14.3%)	12 (85.7%)	14 (28%)	
Poorly differentiated	0 (0%)	2 (100%)	2 (4%)	
Total	4 (8%)	46 (92%)	50	

[Table/Fig-3]: Association of SII with Tumour Grade.
(Fisher-Exact test)

Stage	Low SII (<581)	High SII (>581)	Total cases	p-value
Stage I	0 (0%)	2 (100%)	2 (4%)	0.586
Stage II	2 (20%)	8 (80%)	10 (20%)	
Stage III	1 (5.8%)	16 (94.1%)	17 (34%)	
Stage IV	1 (4.7%)	20 (95.2%)	21 (42%)	
Total	4 (8%)	46 (92%)	50	

[Table/Fig-4]: Association of SII with Tumour Stage.
(Fisher-exact test)

The association of SIRI with tumour grade showed [Table/Fig-5] a distribution, with 94% of cases in the high SIRI group (>0.910) and only 6% in the low SIRI group (<0.910). Well-differentiated tumours dominate (68%), followed by moderately differentiated (28%) and poorly differentiated (4%). The table indicates that high SIRI levels (>0.910) are predominant across all tumour grades, with 94% of the cohort exhibiting elevated SIRI. There is a trend toward higher SIRI in poorly differentiated tumours (100% high SIRI), but the small sample size (2 cases) limits the strength of this observation.

Tumour grade	Low SIRI (<0.910)	High SIRI (>0.910)	Total cases	p-value
Well-differentiated	2 (5.88%)	32 (94.11%)	34 (68%)	1.000
Moderately differentiated	1 (7.14%)	13 (92.85%)	14 (28%)	
Poorly differentiated	0 (0%)	2 (100%)	2 (4%)	
Total	3 (6%)	47 (94%)	50	

[Table/Fig-5]: Association of SIRI with Tumour Grade.
(Fisher-exact test)

Higher SIRI values were associated with more advanced stages [Table/Fig-6]. The analysis of the relationship between tumour stage and SIRI levels in a cohort of 50 cases showed no statistically significant association, as indicated by a p-value of 0.79 from the Fisher's-Exact test. High SIRI levels (>0.910) predominate across all tumour stages, with 84% of cases (42/50) exhibiting elevated SIRI. Specifically, Stage-I showed an equal split (50% low SIRI, 50% high SIRI), but the small sample size (2 cases) limits interpretation. Stages-II, III, and IV had high SIRI proportions (90%, 82.35%, and 85.71%, respectively).

Stage	Low SIRI (<0.910)	High SIRI (>0.910)	Total cases	p-value
Stage I	1 (50%)	1 (50%)	2 (4%)	0.79
Stage II	1 (10%)	9 (90%)	10 (20%)	
Stage III	3 (17.64%)	14 (82.35%)	17 (34%)	
Stage IV	3 (14.28%)	18 (85.71%)	21 (42%)	
Total	8 (16%)	42 (84%)	50	

[Table/Fig-6]: Association of SIRI with Tumour Stage.
(Fisher-exact test)

DISCUSSION

According to the Global Cancer Statistics Database (GLOBOCAN) from the WHO's International Agency for Research on Cancer (WHO/IARC) for the year 2022, New cases 389,846 worldwide. Age-Standardised incidence Rate (ASR): 4.0 per 100,000 people (both sexes all ages). Deaths (2022): 188,438 globally. ASR for mortality: 1.9 per 100,000 people. Ranked 16th in global cancer incidence and 15th in mortality among all cancer sites [4].

India contributes to about 25% of global oral cancer cases, with around 77,000 new cases and 52,000 deaths annually. OSCC is the most common cancer among Indian men and ranks third among women [5,6]. The age standardised incidence rates for oral cancer in India is 9.4/100,000 in men and 5.5/100,000 in women [7].

The state's ASR for oral cancers is estimated at 12 per 100,000, which is higher than the national average [7]. According to a 10-year retrospective study (1997-2006) from tertiary healthcare center, Kolar, oral cavity cancers were among the top two cancersin both males and females. The prevalence of oral squamous carcinoma in Kolar is 29.66%. Specifically, oral cancer constituted 31% of female cancers; 19% of overall cancers in Kolar [8].

In particular, the incidence rate is increasing more sharply in the age groups of the third and fourth decade [9]. Possible causes of this increase include hereditary factors, smoking, alcohol consumption and lifestyle modifications [9]. Men are more likely than women to develop oral cancer. Fifth and sixth decades are the most prevalent age group. Oral cancer has a roughly 50% chance of survival. In the present study mean age group of 60 years was observed with standard deviation of 12.71 years [10].

One major public health problem is still OSCC. It is clear from the research that there aren't many reliable indicators that explicitly pertain to the patient and point to a worse prognosis. Over the past 20 years, OSCC has had a poor 5-year survival rate less than 50%, despite advancements in multidisciplinary teamwork and comprehensive therapy, including surgery, radiation, and chemotherapy [10]. Although the TNM categorisation system is now commonly used to predict survival outcomes and guide treatment strategy selection, patients with the same TNM stage may experience different disease histories [11]. Therefore, identifying reliable and cost effective prognostic markers for OSCC patients is needed to intervene treatment measures and improve overall prognosis.

The SII has been shown to be a strong predictor of a variety of cancer prognosis outcomes, including pancreatic cancer, glioma, cholangiocarcinoma, thyroid cancer and Hepatocellular Carcinoma (HCC) [12-14]. Prior research has examined SII's potential to predict OSCC prognosis, but no reliable results have been published [14]. High preoperative SIRI were also shown to be independent prognostic factors in patients with OSCC, but the data are still very limited [14].

Study done by Diao P et al., showed that for patients with OSCC, a high preoperative SII is a non invasive, inexpensive and effective prognostic predictor and is linked to a bad prognosis [15]. The study by Diao P et al., concluded that for patients with resectable conditions, SII is a novel independent prognostic predictor of survival [15]. In present study also the SII showed a significance with tumour grade which is linked to worst prognosis in OSCC and high SII values are more frequently observed in poorly differentiated tumours, suggesting that SII may serve as a potential prognostic biomarker indicating tumour aggressiveness and poor differentiation in OSCC. Meta-analysis done by Zhang J et al., which included 11 studies, 3,464 patients concluded that elevated SII was significantly associated with worse overall survival, worse disease-free survival, higher risk of T3-T4 tumours (OR 2.47), TNM stage III-IV and poor tumour differentiation. This meta-analysis showed higher SII correlated with advanced tumour stage and grade and worse prognosis [16]. In present study association between SII and tumour stage is not statistically significant (p=0.586) this may be due to small sample size, particularly in early-stage disease. Larger studies may help clarify the prognostic role of SII with respect to tumour staging.

Study done by Song F et al., which included 235 patients with clinical T1-2N0 OSCC cases reported, high pre-op SIRI independently predicted worse overall survival and disease-specific survival, outperforming NLR and MLR [17] which was correlating with the present study as higher the SIRI, higher the grade and stage of disease was present in patients. Study done by Lin J et al., in which prognostic value of SIRI was evaluated in a prospective

cohort consisting of 535 OSCC patients with surgical resection showed risk of death was considerably higher for patients with a higher SIRI than for those with a lower SIRI [18], and highlighted that SIRI significantly enhances prognostic precision when combined with stage and histologic grade. In the present study, there is no statistical significant association between SIRI with grade (p-value 1.0) and stage (p-value 0.79) of disease which can be used as an independent prognostic marker in advanced stages of OSCC. The overall dominance of high SIRI suggests systemic inflammation is a common feature in OSCC. This data provides a foundation for further research into SIRI as a potential biomarker in oncology. Larger studies are needed to determine its prognostic relevance. The lack of significant association indicates SIRI may not differentiate tumour stages in this cohort, though its consistent elevation in Stages II-IV highlights its potential role in cancer-related inflammation. Larger studies with more balanced SIRI distributions and additional clinical data are needed to validate these findings and explore SIRI's prognostic utility. The trend of increasing high SIRI proportions with stage progression suggests a potential relationship that might become significant with a larger sample size.

This present study highlights the potential of SII and significance with the tumour grade. For SIRI although its shows no significance it shows more cases were reflecting higher grade and stage with increase in SIRI values. SII can be used as minimally-invasive biomarkers for assessing the aggressiveness of OSCC. Although the grade and stage did not had statistical significance in SIRI, it was observed that with increase in grade and stage of the disease a high SIRI was observed which showed, higher the grade and stage of disease the inflammatory markers were also high.

Further research with larger population and longitudinal follow-up is warranted to validate these findings and explore their role in guiding therapeutic decisions and prognostic outcome. OSCC has a poor 5 year survival rate that is less than 50% [19] despite various advancements in management including all the modalities. The present study reflects the importance of the prognostic markers in management of the OSCC cases. With SII and SIRI the tumour aggressiveness and its behaviour can be predicted in further management of the cases and can help in prognosis of the disease per se.

Limitation(s)

The limitation of the present study was, single centre study, controls were not taken in the current study, with no standardised cut-off value for both SII and SIRI till date. Due to short duration of study, that is one year the overall survival and disease-free state could not be assessed.

CONCLUSION(S)

The SII is statistically significant and potentially useful biomarker for predicting tumour grade and aggressiveness in OSCC. SIRI did not reach statistical significance in its association with either grade or stage, and larger studies are required to validate its utility. SII and SIRI both showed no statistically significant correlation with tumour stage, possibly due to sample size limitations or overlapping inflammatory responses across stages.

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