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Prognostic Value Of The Systemic Immune-Inflammation Index (SII), Neutrophil-To-Lymphocyte Ratio (NLR), And Platelet-To Lymphocyte Ratio (PLR) In Patients With Oral Squamous Cell Carcinoma (OSCC) - A Systematic Review

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ABSTRACT

BACKGROUND: Cancer represents a major global public health burden, affecting a significant proportion of the population worldwide. Among head and neck malignancies, oral squamous cell carcinoma (OSCC) is the most common histopathological subtype, accounting for nearly 90% of all oral cancers. The tumor microenvironment and systemic inflammatory response play significant roles in tumor progression, treatment response, and patient prognosis.

OBJECTIVE: To evaluate, asses and combine all the current evidence on the prognostic significance of systemic inflammatory biomarkers, that are Systemic Immune-Inflammation Index (SII), Neutrophil-to-Lymphocyte Ratio (NLR), and Platelet-to-Lymphocyte Ratio (PLR) in Oral Squamous Cell Carcinoma.

METHODS: Scientific publications published between 2015 and 2025 in multiple literature databases, such as the PubMed, Scopus, EBSCO, Google Scholar were searched. Preliminary research in well-known literature databases turned up to one thousand two hundred and ninety-six high-calibre academic works. Through application of stringent inclusion and exclusion criteria, we were able to reduce the number of articles from thousands to twelve

RESULTS: The majority of the included studies demonstrated a significant association between elevated SII, NLR, and PLR values and adverse clinical outcomes, including reduced overall survival, disease-free survival, and progression-free survival. Prognostic value of all the three blood markers was observed. By far the most significant correlations being recorded was Systemic immune inflammation index

CONCLUSION: The findings of this review suggest that SII, NLR, and PLR are promising, cost-effective, and readily available prognostic biomarkers in patients with OSCC. However, their prognostic utility may be enhanced when integrated with clinicopathological variables, nutritional indices, composite immune scores.

Introduction:

Cancer represents a major global public health burden, affecting a significant proportion of the population worldwide. India bears a substantial share of the global oral cancer burden, with a continuously increasing incidence of OSCC. Among head and neck malignancies, oral squamous cell carcinoma (OSCC) is the most common histopathological subtype, accounting for nearly 90% of all oral cancers. This rise is primarily attributed to widespread exposure to well-established etiological factors such as tobacco chewing, areca nut consumption, gutkha use, smoking, alcohol intake, and other smokeless tobacco products.[1]

Despite significant advancements in diagnostic modalities and treatment strategies for oral squamous cell carcinoma, mortality and morbidity rates remain alarmingly high. This paradox can be attributed to the easy availability, low cost, and unregulated consumption of tobacco and related products, especially in developing countries. Furthermore, one of the major reasons for the high mortality associated with OSCC is that most patients present at advanced or terminal stages of the disease, owing to lack of awareness, delayed health-seeking behaviour, and negligence toward early symptoms.

Therefore, there is an urgent and overriding need for early diagnosis and timely intervention in oral squamous cell carcinoma. Early detection not only improves survival rates but also reduces treatment-related morbidity, emphasizing the importance of public awareness, regular oral screening, and preventive strategies in high-risk populations.

Research Question

"What is the prognostic value of the Systemic Immune-Inflammation Index (SII), Neutrophil-to Lymphocyte Ratio (NLR), and Platelet-to-Lymphocyte Ratio (PLR) in patients with Oral Squamous Cell Carcinoma (OSCC)?"

Materials and Methods:

Protocol and registration

This systematic review was performed in accordance with (PRISMA 2020) (Figure 1) statement guidelines, the Cochrane Handbook for systematic reviews of interventions and is registered at PROSPERO under the registration code, CRD420251170386

The process of gathering research papers is depicted through a visual flowchart. (Figure 2)

Figure 1: PRISMA Diagram for selected papers

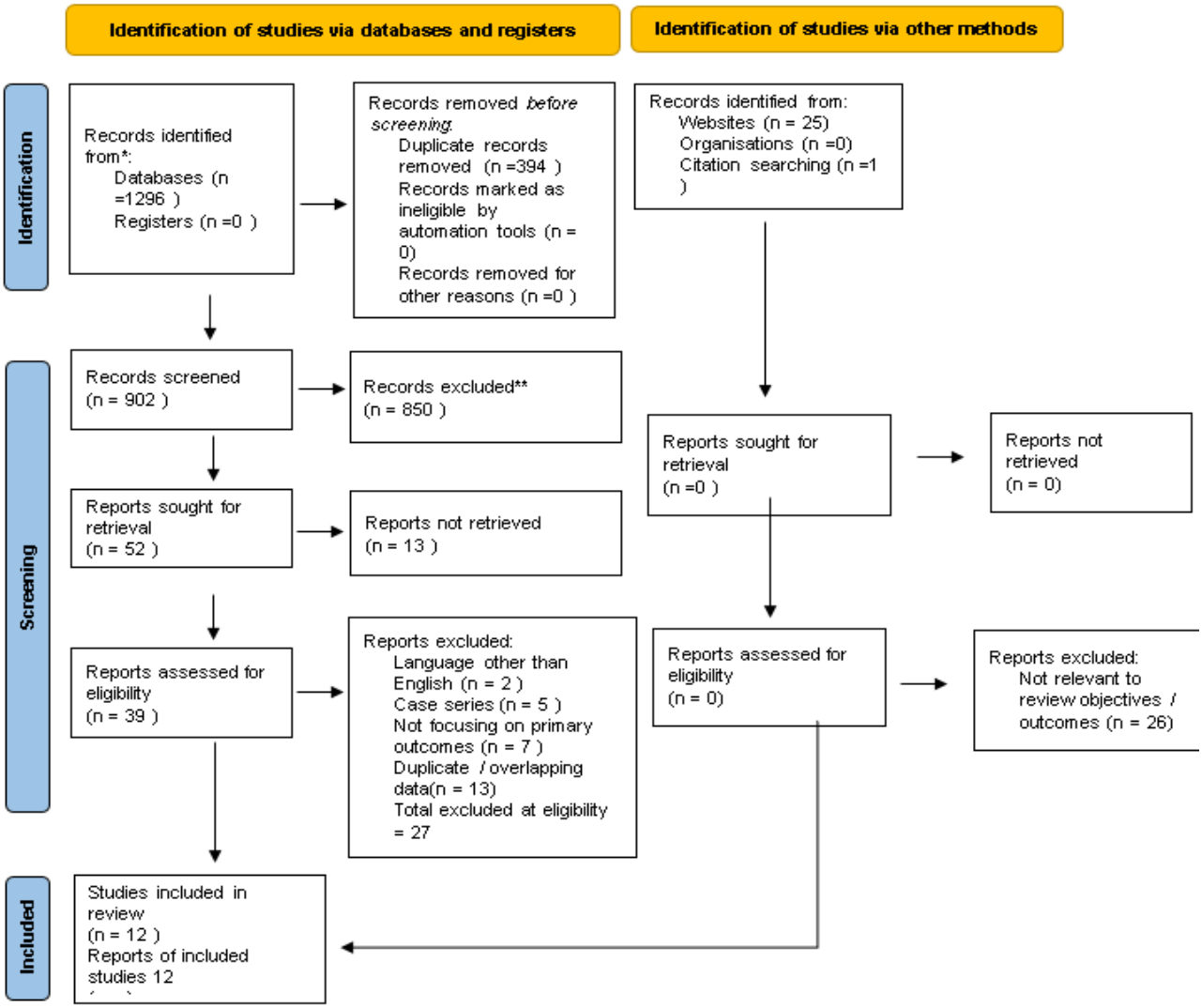
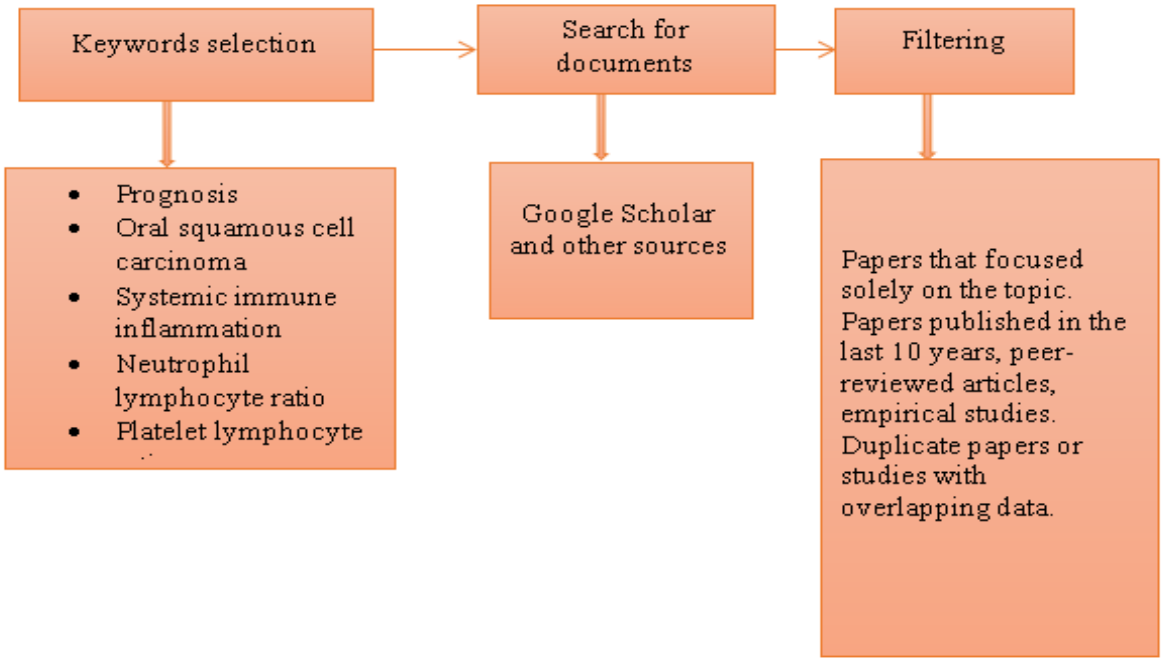


Figure 2: Methodology for Paper collection [source: (self-created)]



Eligibility Criteria:

Inclusion Criteria

Original Research articles such as retrospective, prospective, cohort studies were included. Human studies that involve patients diagnosed with oral squamous cell carcinoma. Articles evaluating Systemic immune inflammation index (SII), Neutrophil to lymphocyte ratio (NLR) and Platelet to lymphocyte ratio (PLR) as prognostic markers. Studies reporting at least one relevant prognostic outcome such as Overall Survival (OS), Disease-Free Survival (DFS), Progression-Free Survival (PFS), and Cancer-Specific Survival (CSS). Articles published in English with full text availability

Exclusion Criteria

Studies were excluded which were randomized control trials, case reports, lacked primary outcome data, duplicated data and articles that were not in English. Studies excluded if not specifically evaluating oral squamous cell carcinoma

Search Strategy:

A comprehensive search strategy was devised to identify relevant studies that meet our inclusion criteria. The following databases were searched: PubMed, Scopus, EBSCO, and Google Scholar. The search was limited to English-language articles published between 2015 to 2025. A combination of keywords and Mesh terms was used to optimize search results. The primary keywords included "oral squamous cell carcinoma, "Systemic Immune inflammation "," neutrophil to lymphocyte ratio", "platelet lymphocyte ratio", "prognosis " and variations thereof. Boolean operators (AND, OR) were applied to refine the search. Additionally, the reference lists of identified articles were examined for potential additional sources.

Screening and Selection of Studies:

Records were first identified through various electronic databases. Prior to screening, a total of 394 records were removed as duplicates on basis of bibliography. No records were excluded using automation tools, and no records were removed for other reasons. After removing duplicate records, 902 records were screened based on their title and abstract. After screening title and abstract, 850 records were excluded leaving 52 records. Full text eligible studies were checked from the 52 records, from that 13 records were not retrieved. After retrieval 39 records were assessed for eligibility out of which 2 records were excluded for language other than English, 5 records as they were case series, 7 records as they were not focusing on primary outcomes and 13 due to duplicate or overlapping study population. Level of agreement, between the two reviewers, calculated by Cohen's kappa (k), was 0.90 for titles and abstracts and 0.92 for full texts.

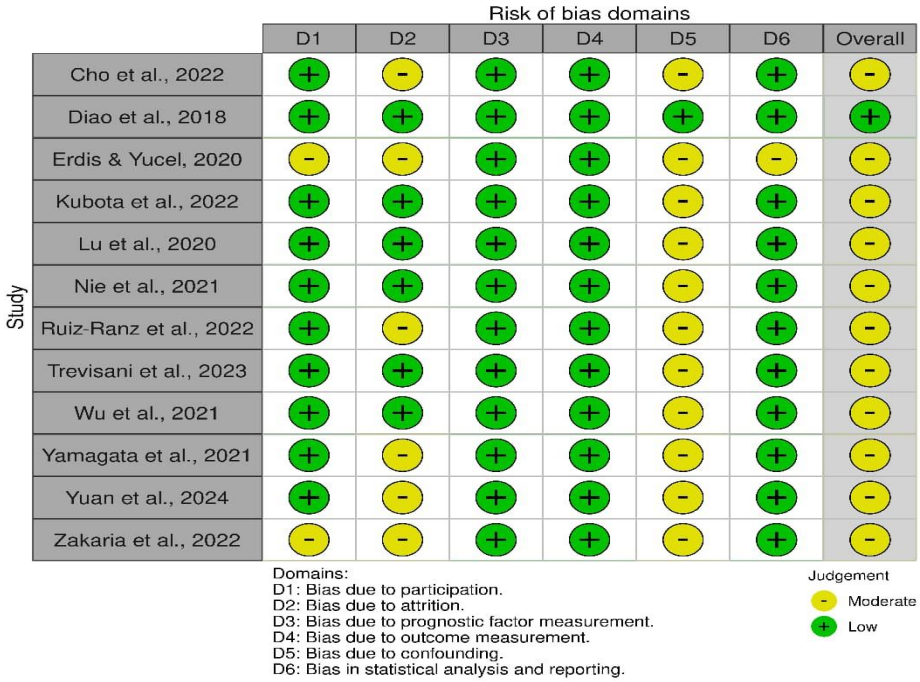
Assessment of the Risk of Bias (ROB) and quality:

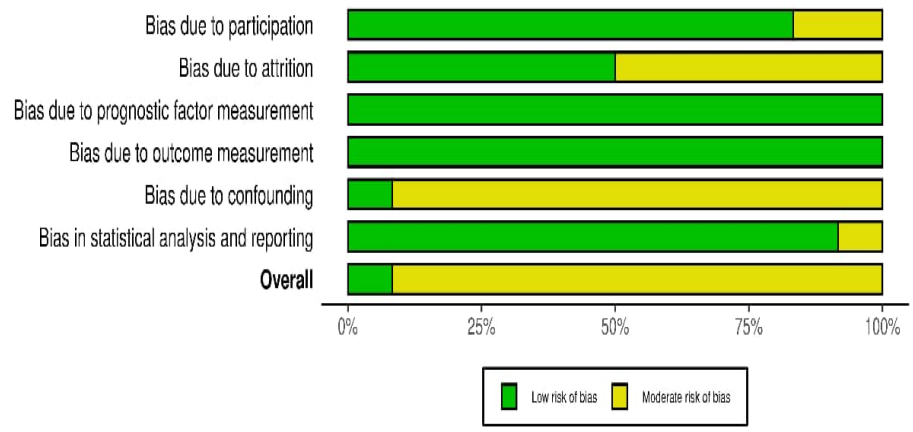
Risk of bias for all twelve studies which were included were evaluated using the **Quality in Prognosis Studies (QUIPS) tool**, which assesses six methodological domains relevant to prognostic research such as study participation, study attrition, outcome measurement, study confounding, prognostic factor measurement and statistical analysis and reporting. Overall, the majority of studies demonstrated a **moderate risk of bias**, primarily due to limitations inherent to retrospective data collection, variation in treatment regimens, and incomplete adjustment for potential confounders such as comorbidities, performance status, lifestyle factors, and HPV status shown in (Figure 3). **Prognostic factor measurement** also consistently scored low risk, as all biomarkers (e.g., NLR, PLR, SII, SIRI, CAR) were derived from routine laboratory tests conducted in standardized hospital settings.

Outcome measurement similarly demonstrated low concern, as survival endpoints (OS, DFS, DSS, or recurrence) were objective and mostly retrieved from hospital and cancer registry records. However, the **study attrition** domain frequently presented moderate risk due to incomplete follow-up or exclusion of cases with missing laboratory values. The **confounding** domain represented the greatest source of bias across studies, as adjustment strategies varied widely and not all clinically relevant covariates were incorporated in multivariable regression analyses. Despite this, most studies used appropriate **statistical modelling**, including Cox proportional hazards regression, Kaplan–Meier survival estimates, ROC analysis, and in some cases external validation, resulting in generally low risk in the analysis and reporting domain.

In summary, **one study was judged to have an overall low risk of bias, while eleven studies were judged as moderate risk**, meaning that results should be interpreted with reasonable confidence but acknowledge the limitations of retrospective prognostic research. No studies were rated as high risk. The predominance of moderate ratings reflects methodological challenges common to observational prognostic investigations rather than critical flaws.

Figure 3: Risk of Bias





Results:

This systematic review tells us about the inflammatory indices such as systemic immune inflammation (SII), neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR).The blood-based markers such as systemic inflammatory indices which can be derived from routine haematological examination.[2] These markers are nowadays more commonly used in oral squamous cell carcinoma as it assesses the inflammation in body, immune status of patient, prognosis of disease and can also help in treatment planning.[3,4,5] Beyond oncology, these haematological indices are also widely applied across various chronic inflammatory conditions as simple, cost-effective markers of systemic inflammatory status.[6] There are many other inflammatory indices other than those which are measured in this systematic review. They are Lymphocyte to monocyte ratio, Prognostic nutritional index, CRP, Glasgow score. These inflammatory indices are significantly related with survival outcomes in individuals with oral squamous cell carcinoma. Poor Overall Survival and shortened Disease-Free Survival were associated with High pre-treatment levels which suggested poor prognosis. Prognostic value of all the three blood markers was observed. By far the most significant correlations being recorded was Systemic immune inflammation index. Elevated systemic immune inflammation index (SII) most consistently correlated with poorer survival, [7,8] and represented as an independent interpreter of overall survival, disease free survival, progression-free survival within multiple cohorts, [9,10,11] especially when evaluated alongside conventional clinicopathologic factors. SII has also been proposed as a promising marker for predicting disease recurrence.[12] Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) showed variable performance. [13,14,15] NLR indicates balance between systemic inflammation and anti tumor immunity.[16] PLR indicates interaction between platelet mediated tumor progression and immune suppression.[17] Cut-off values showed a great variation across studies. There was heterogeneity in threshold values for SII, NLR, and PLR, within studies as they used ROC analysis, median values, or previously published. Standardization of cut-off determination is essential for future clinical implementation. These findings suggest that SII, NLR, and PLR is helpful. However, they might be most valuable when combined with other factors. This includes using multivariable prognostic models or machine learning signatures that also consider nutritional indices, composite immune scores, and detailed tumor characteristics.

- ## Study characteristics:

The study characteristics is explained in the form of table (Figure 4)

Figure 4: Presentation of study characteristics

Study Title	Study design	Participants	Interventions/Exposures	Outcome Measures	Results	Conclusions
Yuan et al., 2024	Prospective preliminary study	68	Systemic immune inflammation index (SII), Neutrophil Lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR)	Progression Free survival	Elevated pre-treatment SII and NLR were independently associated with shorter progression-free survival in patients with OSCC.	SII and NLR were independent prognostic factors
Kubota et al., 2022	Retrospective	183	Systemic immune inflammation index (SII), Neutrophil Lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR)	Overall survival and Disease free survival	High pre-treatment SII was independently associated with reduced disease-free survival, while NLR showed significance only in univariate analysis.	SII was an independent prognostic factor for DFS only. NLR was significant in univariate analysis for DFS

Nie et al., 2021	Retrospective	269	Systemic immune inflammation index (SII), Neutrophil Lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR)	Overall survival and Cancer specific survival	SII remained an independent prognostic factor for overall survival in multivariate analysis, whereas NLR and PLR were not independently associated with survival outcomes.	SII is the key feature: It was found to be an independent prognostic factor for Overall Survival (OS). NLR and PLR were not found to be independent prognostic factors for OS in the multivariate analysis.
Ruiz-Ranz et al., 2022	Retrospective	348	Systemic immune inflammation index (SII), Neutrophil Lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR)	Overall survival and Disease specific survival	Among the evaluated inflammatory markers, only elevated NLR independently predicted poorer overall survival after multivariable adjustment	NLR was the only systemic marker that was an independent predictor of poor OS.
Zakaria et al., 2022	Retrospective	151	Systemic immune inflammation index (SII), Neutrophil Lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR)	Overall survival and Disease free survival	Pre-treatment SII independently predicted disease-free survival, while post-treatment PLR was independently associated with both overall and disease-free survival.	Pre-treatment SII and post-treatment PLR were identified as independent prognostic predictors for DFS. Post-treatment PLR was also an independent predictor for OS (HR 5.261).
Cho et al., 2022	Retrospective	269	Systemic immune inflammation index (SII), Neutrophil Lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR)	Disease specific survival and Progression Free survival	PLR was identified as the only independent inflammatory predictor of disease-specific and progression-free survival in multivariate analysis.	PLR was found to be the only independent predictor among the systemic inflammatory markers (PLR, NLR, SII, SIRI) in the multivariate analysis. PLR was also found to be more strongly

						associated with DSS and PFS in patients who were male, had stage III/IV OSCC, or had lymph node metastasis.
Trevisani et al., 2023	Retrospective	600	Systemic immune inflammation index (SII), Neutrophil Lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR)	Overall survival	Although several inflammatory indices were significant in univariate analysis, only elevated RDW remained independently associated with overall survival in the final multivariate model.	RDW (>14.3%) was the only hematological index identified as an independent risk factor for decreased Overall Survival in the final multivariate model.
Erdis et al., 2020	Retrospective	58	Systemic immune inflammation index (SII), Neutrophil Lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR)	Overall survival and Disease free survival	Elevated SII was the only inflammatory marker independently associated with both overall survival and disease-free survival in patients receiving radiotherapy-based treatment.	SII was the only independent prognostic factor among the three markers for both OS and DFS. The study population was composed entirely of patients who underwent Radiotherapy (RT), mostly postoperative (adjuvant) RT.
Lu et al., 2020	Retrospective	170	Systemic immune inflammation index (SII), Neutrophil Lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR)	Overall survival and Disease free survival	High SII was independently associated with poorer overall and disease-free survival and contributed significantly to prognostic nomogram development.	SII was found to be a novel independent prognostic factor for OS and DFS. The study developed a Nomogram based on Age, LND, and SII for predicting survival. SII showed superiority

						over NLR and PLR based on AUC comparison
Diao et al., 2018	Retrospective	309	Systemic immune inflammation index (SII), Neutrophil Lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR)	Overall survival and Disease free survival	Elevated SII was independently associated with reduced overall and disease-free survival across two validation cohorts.	The study used two independent cohorts. SII was identified as an independent prognostic predictor for patient survival.
Yamagata et al., 2021	Retrospective	205	Systemic immune inflammation index (SII), Neutrophil Lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR)	Overall survival	While SII and NLR demonstrated prognostic associations, only the C-reactive protein to albumin ratio remained independently associated with overall survival.	The study concluded that **CAR** was the **strongest independent prognostic factor** among all markers analyzed
Wu et al., 2021	Retrospective	486	Systemic immune inflammation index (SII), Neutrophil Lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR)	Overall survival and Disease free survival	A composite inflammatory-nutritional risk score including SII independently predicted overall and disease-free survival, showing improved prognostic performance when combined with clinical factors.	Used Machine Learning (LASSO-Cox regression) to develop a prognostic risk score (signature) based on 6 blood parameters (L, P, PNI, LMR, SII, A/G). This Risk Score was an independent prognostic factor for OS and DFS. The final Nomogram integrating the signature with clinical factors showed superior prognostic power.

Discussion:

Comparative studies on blood parameters to determine prognosis in OSCC patients

In studies that developed prognostic nomograms or multivariable Cox models, SII frequently remained in the final model together with key clinicopathologic factors, whereas NLR and PLR were often significant only in univariate analysis or in restricted subgroup models. This pattern suggests that combining neutrophil, platelet and lymphocyte count into a single composite index yields a more robust reflection of the systemic inflammatory–immune balance than either ratio alone. However, when SII, NLR and PLR were compared with an expanded panel of blood parameters, their relative strength became more complex.[18,19] This is further supported by systematic reviews and meta-analyses confirming the superior prognostic performance of SII compared with NLR and PLR in oral cancer.[20,21] Machine learning methods that combined various blood parameters (such as SII) into diagnostic or prognostic profiles enhanced differentiation,[22] suggesting that no single blood marker is universally superior and that using multivariate combinations can provide a more precise assessment of prognosis than individual ratios. Similarly, meta-analytic evidence on NLR and PLR supports their prognostic relevance in oral squamous cell carcinoma, including their association with nodal metastasis, although with greater heterogeneity than SII.[23,24] While elevated pre-treatment SII consistently predicted poorer disease-free or overall survival, post-treatment PLR and platelet count emerged as particularly strong adverse factors in models that incorporated both time points.[25] This suggests that dynamic changes in inflammatory indices in response to therapy may refine risk stratification beyond baseline measurements.

Interobserver agreement

Interobserver agreement is an important but often under-reported aspect when evaluating systemic inflammatory indices as prognostic tools in OSCC. Theoretically, SII, NLR, and PLR should show high reproducibility because they come from standardized automated blood counts. However, variations can still happen due to dissimilarity in laboratory analysers, the schedule of blood sample collection, and pre-analytical factors such as infections, medication use, or recent blood transfusions. When these sources of variability are not controlled or not reported, indirect interobserver reliability—between institutions or investigators—may arise. Future studies should outline their analytic methods in detail, explain quality control processes for haematology analysers, and, when possible, evaluate agreement between laboratories. This approach would build confidence that prognostic classification based on SII, NLR, and PLR is not just statistically significant but also reliable and consistent across different observers and institutions.

Advances in technology

Fast development of analytical and computer technologies is modifying the means of generation, interpretation, and employment of blood, based inflammatory markers in prognostic workflows for OSCC. Contemporary blood cell analysers deliver standard, complete blood counts with strong internal quality controls. This reduces the measurement error for neutrophil, lymphocyte, and platelet counts that are utilized for the calculation of SII, NLR, and PLR. Prognostic role of SII, NLR, and PLR beyond single marker analysis have been broadened due to development in radiomics, artificial intelligence, and machine learning. Deep learning models can combine systemic indices with detailed imaging data, like optical coherence tomography or cross-sectional imaging which creates composite prognostic scores that provide excellent discrimination.

Conclusion:

This systematic review shows that simple systemic inflammatory markers especially the systemic immune inflammation index (SII) that hold substantial promise as adjunctive prognostic tools in oral squamous cell carcinoma. While traditional factors such as stage, depth of invasion, and nodal status remain central,[26] incorporating SII, and in selected scenarios NLR and PLR, can sharpen risk stratification and support more individualized patient counselling and treatment planning. However, the predominance of retrospective single-centre data, lack of standardized cut-offs, and limited external validation mean that these indices cannot yet replace established prognostic systems and should currently be viewed as complementary markers awaiting robust prospective confirmation. With carefully designed future studies addressing these gaps, SII-, NLR- and PLR-based approaches could become integral components of low-cost, precision prognostication in OSCC, particularly valuable in settings where access to advanced molecular testing is limited.

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Conflicts of interest:

There are no conflicts of interest.

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