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Original Article

Oncology Section

Evaluating Preoperative Systemic Inflammatory Markers as Predictors of Cervical Metastasis in Oral Squamous Cell Carcinoma: A Cross-sectional Study

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ABSTRACT

Introduction: Oral Squamous Cell Carcinoma (OSCC) is a leading malignancy in India, contributing to nearly one-third of global cases. Cervical lymph node metastasis is the most critical prognostic factor; however, reliable preoperative predictors remain limited. C-Reactive Protein (CRP) is a direct inflammatory marker, whereas Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) are inflammation based haematological indices that have shown prognostic relevance in various malignancies.

Aim: To evaluate and correlate preoperative serum CRP, NLR, and PLR with cervical lymph node metastasis in patients with primary OSCC.

Materials and Methods: This cross-sectional observational study was conducted in the Department of Oral and Maxillofacial Surgery, Sharad Pawar Dental College and Hospital, Datta Meghe Institute of Higher Education and Research, Sawangi (Meghe) Maharashtra, India, from October 2020 to May 2022. Forty patients with histopathologically confirmed OSCC undergoing surgical excision with modified radical neck dissection were included. Preoperative CRP and Complete Blood Counts (CBC) were obtained within one week prior to surgery. NLR and PLR were calculated from haematological parameters. Cervical metastasis was confirmed by final histopathology. Statistical analysis was performed using Pearson's correlation coefficient (r-value). Association between inflammatory markers (CRP, NLR, PLR) and cervical lymph node metastasis was assessed using Chi-square test. A p-value <0.05 was considered statistically significant.

Results: The age of the patients ranged from 35 to 74 years, with a mean age of 54.5 years. There was a marked male predominance, with 31 males (77.5%) and 9 females (22.5%), resulting in a male-to- female ratio of approximately 3.4:1. of whom 13 (32.5%) had cervical metastasis. Elevated CRP, PLR, and NLR were observed in 18 (45%), 21 (52.5%), and 31 (77.5%) patients, respectively. No statistically significant association was observed between CRP (r=-0.14, p=0.37), PLR (r=-0.02, p=0.92), or NLR (r=-0.04, p=0.81) and cervical metastasis.

Conclusion: Preoperative CRP, NLR, and PLR did not show a significant association with cervical metastasis in OSCC. Although these markers are inexpensive and readily available, their standalone predictive value appears limited. Larger multicentric studies are warranted to validate their prognostic role.

Keywords: Haematological indices, Inflammation-based markers, Lymph node involvement, Oral cancer, Prognosis

INTRODUCTION

The OSCC represents a major public health challenge in India, accounting for nearly 30% of all cancers nationwide and approximately one-third of global cases. According to the 2020 cancer registry, India recorded 119,992 active cases, with an incidence rate of 10.5 per 100,000 adults [1]. OSCC disproportionately affects men and is characterised by aggressive local invasion and metastasis to cervical lymph nodes, predominately levels I-III. Although distant metastasis occurs in only 4.8% of cases, cervical node involvement reduces survival by almost 50% [2], contributing to poor outcomes such as locoregional recurrence, secondary primaries, and an overall five-year survival rate of just 68% following surgical resection [3].

Traditional prognostic tools, including Tumour, Lymph Node and Metastasis (TNM) staging and histopathological grading, remain central to treatment planning but suffer from interobserver variability and limited predictive accuracy. Two tumours of identical stage and grade may follow markedly different clinical courses, underscoring the need for more reliable prognostic biomarkers. Among available prognostic indicators, cervical lymph node metastasis remains the most critical determinant of survival [4]. However, existing tumour markers lack sensitivity and are often impractical for routine use due to cost and complexity [5].

Current imaging modalities also fail to detect micrometastasic disease, leaving surgeons and clinicians without dependable preoperative predictors of regional metastasis, adjuvant therapy requirements, or long-term outcomes. Novel biomarkers could potentially reduce unnecessary surgical interventions in node-negative patients. For instance, proteomic and genomic approaches - such as four protein signatures and microarray - based survival analyses - show promise but remain impractical in most clinical settings [6].

Mounting evidence suggests a pivotal role of the Systemic Inflammatory Response (SIR) in tumour initiation, progression, and metastasis [7]. Cancer-driven inflammation alters haematological indices, including neutrophils, lymphocytes, platelets, and cytokines, thereby fostering angiogenesis, Deoxyribonucleic Acid (DNA) damage, immune evasion, and tumour proliferation [8]. Among these mediators, CRP, induced by Interleukin-6 (IL-6) and Tumour Necrosis Factor (TNF-α), has been repeatedly implicated in OSCC [9].

Readily measurable indices such as the NLR and PLR provide simple, cost-effective surrogates of SIR and have shown prognostic value in several malignancies. However, their predictive role in cervical, metastasis among OSCC patients remains underexplored.

The objective of the present study was to evaluate and correlate preoperative systemic inflammatory markers, serum CRP, NLR, and

PLR, with cervical lymph node metastasis in patients diagnosed with primary OSCC.

MATERIALS AND METHODS

This cross-sectional observational study was conducted in the Department of Oral and Maxillofacial Surgery, Sharad Pawar Dental College and Hospital, Datta Meghe Institute of Higher Education and Research, Sawangi (Meghe) Maharashtra India, from October 2020 to May 2022, following approval from the Institutional Ethics Committee (IEC No. DMIMS(DU)/IEC/2020-21/2419). Written informed consent was obtained from all participants.

Inclusion criteria

- Primary, untreated OSCC confirmed by incisional biopsy;
- Eligibility for surgical resection with modified radical neck dissection.

Exclusion criteria

- Non OSCC oral malignancies;
- Prior chemoradiotherapy;
- Clinical or laboratory evidence of active infection or systemic inflammatory disorders;
- Haematological or bleeding disorders.

Study Procedure

Comprehensive clinicopathological data of forty patients were recorded, including: age, gender, tumour site, extent, size, TNM staging [10], histological grade [11] and number of excised and positive lymph nodes.

Preoperative blood samples were collected within one week prior to surgery. Laboratory tests included:

- CRP measurements using the VITROS Integrated System 5600 with an immunoturbidimetric assay.
- CBC performed using the Beckman Coulter DXH 800 haematology analyser.

From CBC data, the following indices were derived:

- NLR=Neutrophil count/Lymphocyte count.
- PLR=Platelet count/Lymphocyte count.

Cut-off values were adopted from previously published literature: CRP ≥5mg/L, NLR ≥5, and PLR ≥ 200 [12-14].

All patients underwent surgical excision of the primary lesion with modified radical neck dissection, followed by reconstruction. Histopathological examination served as the reference standard for confirming nodal involvement.

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 27.0. Pearson's correlation coefficient (r) was used to assess associations between inflammatory markers and cervical metastasis. Association between inflammatory markers (CRP, NLR, PLR) and cervical lymph node metastasis was assessed using Chi-square test. A p-value <0.05 was conside red statistically significant.

RESULTS

A total of 40 patients with histopathologically confirmed primary OSCC who underwent comprehensive surgical staging were included in the study.

Demographic and Clinicopathological Characteristics

The age of the patients ranged from 35 to 74 years, with a mean age of 54.5 years. Patient aged more than 50 years constituted the majority of the study population 23 (57.5%), while 17 patients (42.5%) were aged 50 years or younger. There was a marked male predominance, with 31 males (77.5%) and 9 females (22.5%), resulting in a male-to- female ratio of approximately 3.4:1.

Regarding tumour location, the buccal mucosa was the most commonly affected site 18 (45%), followed by the tongue 14 (35%), alveolus 5 (12.5%), and floor of the mouth 3 (7.5%). Tumour size assessment revealed that 22 patients (55%) had tumours measuring ≤4 cm, whereas 18 patients (45%) presented with tumours larger than 4 cm.

Based on TNM staging, 15 patients (37.5%) were categorised under early-stage disease (Stage I-II), while 25 patients (62.5%) had advanced-stage disease (Stage III-IV). Histopathological grading demonstrated that 19 cases (47.5%) were well-differentiated squamous cell carcinomas, 16 cases (40%) were moderately-differentiated, and five cases (12.5%) were poorly-differentiated.

The mean number of lymph nodes excised per patient was 18.6±4.2. Cervical lymph node metastasis was identified on final histopathological examination in 13 patients (32.5%), while 27 patients (67.5%) had no evidence of nodal metastasis. The distribution of demographic and clinicopathological parameters is summarised in [Table/Fig-1].

Parameters	Category	n (%)
Age (years)	≤ 50	17 (42.5)
	>50	23 (57.5)
Gender	Male	31 (77.5)
	Female	9 (22.5)
Tumour site	Buccal mucosa	18 (45.0)
	Tongue	14 (35.0)
	Alveolus	5 (12.5)
	Floor of mouth	3 (7.5)
Tumour size	≤ 4 cm	22 (55.0)
	>4 cm	18 (45.0)
TNM stage	Stage I-II	15 (37.5)
	Stage III-IV	25 (62.5)
Histological grade	Well-differentiated	19 (47.5)
	Moderately-differentiated	16 (40.0)
	Poorly-differentiated	5 (12.5)
Lymph nodes excised	Mean±SD	18.6±4.2
Positive lymph nodes	Present	13 (32.5)
	Absent	27 (67.5)

[Table/Fig-1]: Distribution of clinicopathological parameters.

Association between CRP Levels and Cervical Metastasis

Elevated preoperative serum CRP levels (≥5 mg/L) were observed in 18 patients (45%), while 22 patients (55%) had CRP values below the cut-off. Among patients with elevated CRP levels, 4 patients (22.2%) had cervical lymph node metastasis, whereas 14 patients (77.8%) did not. No statistically significant association was observed between preoperative CRP levels and cervical lymph node metastasis (r=-0.14, p=0.37) [Table/Fig-2].

Serum CRP level	Cervical metastasis present n (%)	Cervical metastasis absent n (%)	Total n (%)	r-value	p-value
Elevated (≥5 mg/L)	4 (22.2)	14 (77.8)	18 (45.0)	-0.14	0.37
Normal (<5 mg/L)	9 (40.9)	13 (59.1)	22 (55.0)	-	-
Total	13 (32.5)	27 (67.5)	40 (100)		

[Table/Fig-2]: Association between preoperative serum CRP levels and cervical lymph node metastasis in OSCC

Association between PLR and Cervical Metastasis

An elevated (PLR ≥ 200) was observed in 21 patients (52.5%), while 19 patients (47.5%) had PLR values below the cut-off. Cervical metastasis was present in 6 patients (28.6%) with elevated PLR

and absent in 15 patients (71.4%). The association between PLR and cervical lymph node metastasis was not statistically significant (p=0.92, r=-0.02) [Table/Fig-3].

PLR level	Cervical metastasis present n (%)	Cervical metastasis absent n (%)	Total n (%)	r-value	p-value
Elevated (≥200)	6 (28.6)	15 (71.4)	21 (52.5)	-0.02	0.92
Normal (<200)	7 (36.8)	12 (63.2)	19 (47.5)	-	-
Total	13 (32.5)	27 (67.5)	40 (100)	-	-

[Table/Fig-3]: Association between preoperative PLR and cervical lymph node metastasis in OSCC

Association between NLR and Cervical Metastasis

An elevated NLR ≥5 was noted in 31 patients (77.5%), while 9 patients (22.5%) had NLR values within the normal range. Cervical lymph node metastasis was observed in 11 patients (35.5%) with elevated NLR and in two patients (22.2%) with normal NLR values. No statistically significant association was found between preoperative NLR and cervical lymph node metastasis (p=0.81, r=-0.04) [Table/Fig-4].

NLR level	Cervical metastasis Present n (%)	Cervical metastasis absent n (%)	Total n (%)	r-value	p-value
Elevated (≥5)	11 (35.5)	20 (64.5)	31 (77.5)	-0.04	0.81
Normal (<5)	2 (22.2)	7 (77.8)	9 (22.5)	-	-
Total	13 (32.5)	27 (67.5)	40 (100)	-	-

[Table/Fig-4]: Association between preoperative NLR and cervical lymph node metastasis in OSCC

DISCUSSION

Cervical lymph node metastasis remains the most important prognostic determinant in OSCC, significantly influencing survival outcomes and treatment planning [4]. Accurate preoperative prediction of nodal involvement is therefore crucial; however, conventional imaging modalities and clinical examination often fail to detect occult metastasis, necessitating the exploration of reliable, cost-effective biomarkers [5,6].

The present study evaluated the association between preoperative systemic inflammatory markers- CRP, NLR, and PLR (inflammation-based indices)- and cervical lymph node metastasis in patients with primary OSCC. Although elevated levels of these markers were frequently observed, no statistically significant correlation with cervical metastasis was identified.

Systemic inflammation has been increasingly recognized as a key contributor to tumour initiation, progression, angiogenesis, and metastasis [7,8]. CRP, an acute-phase protein synthesised by hepatocytes in response to inflammatory cytokines such as IL-6 and TNF-α, reflects the magnitude of SIR and has been associated with adverse oncological outcomes in various malignancies [9]. In OSCC, Acharya S et al., demonstrated that elevated preoperative CRP levels were associated with poorer survival outcomes and increased likelihood of nodal metastasis [12]. Similarly, Huang SF et al., reported that combined evaluation of CRP and squamous cell carcinoma antigen improved risk stratification in oral cancer patients [14]. However, in the present study, elevated CRP levels did not show a statistically significant association with cervical lymph node metastasis, suggesting that CRP alone may not be a reliable predictor of nodal disease [15].

Inflammation-based haematological indices such as NLR and PLR have gained attention due to their simplicity and availability from routine blood investigations. Neutrophils promote tumour progression by secreting proangiogenic factors, suppressing cytotoxic lymphocyte activity, and facilitating immune evasion, while lymphocytes play a critical role in antitumour immunity [9]. Consequently, an elevated NLR reflects a shift toward a pro-tumour inflammatory state. Previous studies have reported conflicting results regarding the prognostic value of NLR in OSCC. Nakashima H et al. demonstrated that elevated pre-treatment NLR predictor poor response to chemoradiotherapy and reduced survival [16], whereas Park YM et al., reported its usefulness as part of a composite inflammatory scoring system [17]. In contrast, the present study did not demonstrate a significant association between NLR and cervical metastasis, consistent with findings reported by Tazeen S et al., [18].

Platelets contribute to tumour growth and metastasis by promoting angiogenesis, shielding circulating tumour cells from immune surveillance, and facilitating extravasation at metastasis sites. Accordingly, PLR has been proposed as a potential prognostic marker in various solid tumours. Acharya S et al., reported that PLR was superior to NLR in predicting lymph node metastasis in OSCC [13]. However, similar to the findings of Tazeen S et al., the present study found no statistically significant association between PLR and cervical lymph node metastasis [18]. Recent studies and meta-analyses have suggested that while PLR may have prognostic value for survival outcomes, its role in predicting nodal involvement remains inconsistent [19-21]. Additionally, systemic inflammatory markers are influenced by multiple factors beyond biology, including subclinical infections, nutritional status, and perioperative physiological stress, which may confound their predictive accuracy [7,9]. The study highlights the complexity of inflammatory pathways in OSCC and underscores that no single biomarker may be sufficient to predict cervical metastasis reliably. Recent literature suggests that composite inflammation-based scoring systems or multimodal predictive models integrating clinicopathological parameters with molecular markers may offer improved prognostic accuracy [6,19].

Limitation(s)

The present study has certain limitations that should be acknowledged. The relatively small sample size and single-centre study design may limit the generalisability of the findings. Additionally, only selected inflammatory markers were evaluated; other inflammatory and immunological markers such as erythrocyte sedimentation rate, ILs, and TNF-α were not included, which may have provided a more comprehensive assessment of the SIR.

CONCLUSION(S)

The present cross-sectional observational study demonstrates that preoperative CRP, NLR, and PLR are not significantly associated with cervical metastasis in OSCC. While systemic inflammatory markers are attractive due to their low cost, accessibility, and non invasive nature, their standalone predictive value for nodal disease appears limited. Nonetheless, these indices may still have utility when integrated with established clinical, radiological, and pathological parameters. Larger, multicentre trials are warranted to validate their prognostic relevance and to explore their role in risk stratification, treatment planning, and postoperative surveillance in OSCC.

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