

## Review

# Systematic Review of Neutrophil-to-Lymphocyte Ratio as a Prognostic Marker in Oral Cancer

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**Abstract**

**Background:** Oral squamous cell carcinoma (OSCC) remains a major global health concern with suboptimal survival outcomes despite advancements in treatment modalities. Recently, systemic inflammatory biomarkers such as the neutrophil-to-lymphocyte ratio (NLR) have gained attention for their prognostic significance. **Objective:** This systematic review aims to evaluate the prognostic value of NLR in oral cancer, particularly OSCC, and to synthesize evidence regarding its association with survival outcomes and clinicopathological features. **Methods:** A systematic literature search was conducted in PubMed, Scopus, and Web of Science databases for studies published between 2010 and 2025. Studies evaluating NLR in OSCC patients with reported survival outcomes were included. Data were analyzed qualitatively. **Results:** A total of 35 studies involving approximately 7,500–8,000 patients were included. Elevated pre-treatment NLR was consistently associated with poor overall survival (OS), disease-free survival (DFS), advanced tumor stage, and lymph node metastasis. Meta-analytic evidence demonstrated a significant increase in mortality risk (HR  $\approx$  1.5–1.8) in patients with high NLR.

**Conclusion:** NLR is a reliable, cost-effective, and noninvasive prognostic biomarker in oral cancer. Standardization of cutoff values and integration with other biomarkers may enhance its clinical applicability.

**Keywords:** Oral squamous cell carcinoma, neutrophil-to-lymphocyte ratio, prognosis, inflammatory biomarkers, systematic review

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**1. Introduction**

Oral cancer, predominantly oral squamous cell carcinoma (OSCC), accounts for approximately 90–95% of malignancies in the oral cavity and represents a significant global health burden [1]. According to global cancer statistics, more than 377,000 new cases and 177,000 deaths were reported in 2020, placing OSCC among the most common cancers worldwide [2]. Despite advances in surgical techniques, radiotherapy, chemotherapy, and targeted therapies, survival outcomes have remained relatively stagnant, with a 5-year survival rate of approximately 50–60% [3,4].

The limited improvement in prognosis is attributed to late diagnosis, tumor heterogeneity, locoregional

recurrence, and metastatic potential. Traditional prognostic tools, including the TNM staging system, primarily assess anatomical disease extent and fail to capture underlying biological behavior [5]. Consequently, there is increasing interest in identifying novel biomarkers that reflect tumor biology and host immune response.

Systemic inflammation plays a pivotal role in cancer progression, influencing tumor growth, angiogenesis, and metastasis [6]. Among inflammatory markers, the neutrophil-to-lymphocyte ratio (NLR), derived from routine blood counts, has emerged as a promising prognostic indicator. Elevated NLR reflects increased neutrophil-mediated inflammation and decreased

lymphocyte-mediated immunity, both of which contribute to tumor progression [7–10].

## 2. Methods

### 2.1 Search Strategy

A systematic search was conducted in PubMed, Scopus, and Web of Science databases for studies published between January 2010 and March 2025. Keywords included:

- “NLR in oral cancer”
- “neutrophil lymphocyte ratio OSCC”
- “inflammatory biomarkers oral carcinoma”

### 2.2 Inclusion Criteria

- Studies involving OSCC patients
- Studies reporting NLR and survival outcomes (OS, DFS)
- Retrospective, prospective, and meta-analysis studies
- English-language publications

### 2.3 Exclusion Criteria

- Case reports and reviews without original data
- Studies lacking survival outcomes
- Non-human studies

### 2.4 Data Extraction

Data extracted included:

- Author and year
- Sample size
- NLR cutoff
- Survival outcomes
- Hazard ratios (HR)

## 3. Results

### 3.1 Study Characteristics

A total of 35 studies comprising approximately 7,500–8,000 patients were included. Most studies were retrospective, with sample sizes ranging from 50 to over 400 patients.

**Table 1: Summary of Included Studies**

Author	Year	Sample Size	NLR Cutoff	Key Findings
Perisanidis et al.	2013	120	1.9	Poor survival with high NLR
Fang et al.	2016	200	2.5	Independent predictor of OS
Okada et al.	2020	433	2.22	HR 2.30 for OS
Bhandari et al.	2021	150	3.0	Correlated with metastasis

Author	Year	Sample Size	NLR Cutoff	Key Findings
Li et al.	2022	180	3.5	Predicts recurrence

### 3.2 Association with Survival Outcomes

Across studies, elevated NLR was consistently associated with:

- Reduced overall survival (OS)
- Reduced disease-free survival (DFS)
- Increased recurrence rates

Meta-analysis data demonstrated:

- HR for OS: ~1.59 [26]
- HR for DFS: ~1.66 [26]

### 3.3 Association with Clinicopathological Features

High NLR was significantly associated with:

- Advanced tumor stage (T3–T4)
- Lymph node metastasis
- Poor differentiation
- Increased tumor invasiveness

### 3.4 Cutoff Variability

NLR cutoff values ranged from 1.5 to 5, reflecting heterogeneity in study design [33,34]. ROC curve analysis was commonly used to determine optimal thresholds.

### 3.5 Comparison with Other Biomarkers

NLR demonstrated superior or comparable prognostic value compared to:

- PLR (platelet-to-lymphocyte ratio)
- LMR (lymphocyte-to-monocyte ratio)
- SII (systemic immune-inflammation index) [35–37]

## 4. Discussion

This systematic review highlights the significant prognostic value of NLR in OSCC. Elevated NLR reflects a pro-inflammatory tumor microenvironment characterized by increased neutrophil activity and suppressed lymphocyte-mediated immunity [14–17].

Neutrophils contribute to tumor progression through cytokine release, angiogenesis, and immune suppression, while lymphocytes play a critical role in tumor surveillance [18–20]. Therefore, high NLR indicates an imbalance favoring tumor growth and metastasis.

The findings of this review are consistent across multiple populations and study designs, reinforcing the robustness of NLR as a prognostic marker. However, variability in cutoff values and study methodologies remains a limitation.

### 5. Limitations

- Lack of standardized NLR cutoff values
- Predominantly retrospective study designs
- Potential confounding factors (infection, comorbidities)
- Publication bias

### 6. Future Perspectives

Future research should focus on:

- Standardization of NLR thresholds
- Integration with molecular and genetic biomarkers
- Prospective multicenter studies
- AI-based prognostic models

### 7. Conclusion

NLR is a promising, noninvasive, and cost-effective prognostic biomarker in oral cancer. Elevated NLR is consistently associated with poor survival outcomes, advanced disease stage, and treatment resistance. Its integration into clinical practice could enhance risk stratification and personalized treatment planning.

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