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Original Research Article

THE ROLE OF LYMPH NODE RATIO IN PREDICTING SURVIVAL OUTCOMES IN ORAL SQUAMOUS CELL CARCINOMA

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ABSTRACT

Background: The lymph node ratio (LNR), defined as the ratio of positive lymph nodes to the total number of dissected lymph nodes, has emerged as a potential prognostic indicator in oral squamous cell carcinoma (OSCC). This study aimed to evaluate the prognostic significance of LNR in predicting outcomes, including overall survival (OS) and disease-free survival (DFS) in OSCC patients.
Materials and Methods: A retrospective analysis was conducted on 241 patients with histologically confirmed OSCC who underwent surgical resection with curative intent and cervical lymph node dissection. Patients were categorized into two groups based on LNR: low LNR (≤0.20) and high LNR (>0.20). Survival analysis was performed using Kaplan-Meier curves, and Cox proportional hazards regression models were used to identify prognostic factors for OS and DFS. Receiver Operating Characteristic (ROC) curve analysis was conducted to assess the prognostic accuracy of LNR.
Results: Patients with a high LNR had significantly worse survival outcomes compared to those with a low LNR. The 3-year OS rate was 42.4% in the high LNR group versus 78.7% in the low LNR group ($p < 0.001$), while the 3-year DFS rate was 35.2% versus 70.5%, respectively ($p < 0.001$). Multivariate analysis confirmed high LNR as an independent predictor of poor OS (HR: 1.72, 95% CI: 1.21–2.43, $p = 0.002$) and DFS. Other significant factors included age, histological grade, depth of invasion, perineural invasion, and lymphovascular invasion. ROC curve analysis showed that LNR had a high prognostic accuracy for predicting survival outcomes.
Conclusion: The LNR is a significant prognostic factor in OSCC, providing additional information beyond the traditional TNM staging system. Incorporating LNR into routine pathological assessment may improve risk stratification and guide treatment planning, particularly for patients at higher risk of recurrence and poorer survival.
Keywords: Oral squamous cell carcinoma(OSCC), Lymph node ratio(LNR), Prognostic factor(PF), Survival analysis(SA), Overall survival(OS), Disease-free survival(DFS), Cox regression analysis(CRA).

INTRODUCTION

Oral squamous cell carcinoma (OSCC) represents approximately 90% of all oral cancers and is the sixth most common cancer worldwide, with an estimated annual incidence of over 300,000 new cases.[1] Despite advances in surgical techniques, chemotherapy, and radiotherapy, the overall 5-year survival rate for OSCC remains around 50-60%, which is largely attributable to late-stage diagnosis and regional lymph node metastasis.[2]

Lymph node involvement is one of the most critical prognostic factors in OSCC, with studies indicating that patients with lymph node metastasis have a 50% reduction in survival compared to those without nodal involvement.[3] The current TNM (Tumor, Node, Metastasis) staging system classifies nodal involvement based on the size, number, and location of metastatic nodes. While this staging system remains the gold standard for prognostication, it does not always provide a comprehensive assessment of nodal disease burden, as it fails to account for variations in the extent of lymphadenectomy and the actual number of dissected lymph nodes.[4]

The concept of the lymph node ratio (LNR), defined as the ratio of metastatic (positive) lymph nodes to the total number of dissected lymph nodes, has gained traction as a more accurate prognostic indicator in recent years. Several studies across different cancers, including breast, gastric, and colorectal cancers, have demonstrated that a higher LNR correlates with poorer survival outcomes.[5,6] In OSCC, LNR has been shown to outperform conventional nodal status in predicting patient outcomes, with research indicating that an LNR > 0.20 is associated with a significantly worse 5-year overall survival rate.[7]

For instance, a retrospective study involving 283 OSCC patients found that those with an LNR > 0.20 had a 5-year overall survival rate of 37%, compared to 67% in patients with an LNR ≤ 0.20.[8] Another multicenter study demonstrated that LNR is an independent predictor of disease-free survival, even after adjusting for other prognostic factors such as age, tumor size, and extranodal extension.[9] These findings suggest that LNR could serve as a valuable tool for risk stratification, particularly in cases where the traditional TNM staging system may not fully capture the extent of nodal disease.

Given the limitations of the TNM system and the emerging evidence supporting the prognostic value of LNR, there is a growing need to explore the significance of LNR in OSCC comprehensively. By evaluating the prognostic role of LNR, clinicians can achieve a more accurate assessment of patient prognosis, which is crucial for tailoring adjuvant therapy, optimizing treatment strategies, and ultimately improving patient outcomes. Therefore, this study aimed to assess the prognostic significance of LNR in predicting outcomes in OSCC patients, providing further evidence for its potential integration into clinical practice. Understanding the role of LNR could lead to a paradigm shift in the management of OSCC, enabling more personalized and effective treatment approaches.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective cohort study conducted at a tertiary care center specializing in head and neck oncology, for a period of 1 year from July 2022 to June 2023 in the department of Pathology. The study protocol was approved by the Institutional Review Board (IRB) and Ethics Committee.

Study Population and Sample Size

Patients diagnosed with oral squamous cell carcinoma (OSCC) who underwent surgical resection with curative intent, including neck dissection, were included in the study. The inclusion criteria were histologically confirmed OSCC, undergoing primary tumor resection with cervical lymph node dissection, and the availability of complete pathological data on lymph node status. Patients were excluded if they presented with distant metastasis (M1 stage), had incomplete medical records or follow-up data, or had received previous treatment for OSCC, such as radiation or chemotherapy.

The sample size was determined based on the prevalence of OSCC in India, which accounts for 30-40% of head and neck cancers [10]. Considering an effect size of 0.3 to 0.5, a hazard ratio of 1.5 to 2.0 for high versus low LNR groups, and an event rate of 20-30% over 5 years a sample size of 241 patients was calculated to achieve 80% power with a 95% confidence level (α = 0.05).[11] This range ensures sufficient statistical power to detect prognostic differences in survival outcomes between LNR groups.

Data Collection

Data were extracted from electronic medical records and pathology reports, including demographic information such as age, gender, and smoking or alcohol history. Tumor characteristics were recorded, including tumor size, location, histological grade, depth of invasion, and the presence of perineural or lymphovascular invasion. Details of nodal status were collected, covering the total number of dissected lymph nodes, the number of positive lymph nodes, extranodal extension, and the pathologic TNM stage according to the 8th edition of the AJCC staging system. Treatment details, such as the type of surgery and whether adjuvant radiotherapy or chemotherapy was administered, were also documented. Finally, follow-up data were gathered to assess recurrence, disease-free survival (DFS), and overall survival (OS), with a median follow-up period of 36 months.

Calculation of Lymph Node Ratio (LNR)

The lymph node ratio (LNR) was calculated as the number of positive lymph nodes divided by the total number of dissected lymph nodes (LNR = Number of positive lymph nodes / Total number of dissected lymph nodes). Based on the LNR values, patients were categorized into two groups: those with a low LNR (≤0.20) and those with a high LNR (>0.20). The cut-off value of 0.20 was determined based on evidence from previous study demonstrating its prognostic significance in oral squamous cell carcinoma and was further validated using Kaplan-Meier survival analysis to assess differences in survival outcomes between the groups.[12]

Outcome Measures

The primary outcome was overall survival (OS), defined as the time from surgery to death from any cause. The secondary outcome was disease-free survival (DFS), defined as the time from surgery to the first recurrence or death.

Statistical Analysis

Statistical analyses were performed using SPSS Version 25.0. Descriptive analysis was conducted, where continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range), while categorical variables were expressed as frequencies and percentages. For survival analysis, Kaplan-Meier survival curves were generated for overall survival (OS) and disease-free survival (DFS), and the log-rank test was used to compare survival rates between the low LNR and high LNR groups. Univariate and multivariate analyses were carried out using Cox proportional hazards regression models to identify prognostic factors for OS and DFS, with variables showing p-values < 0.05 in the univariate analysis being included in the multivariate analysis. Additionally, receiver operating characteristic (ROC) curve analysis was performed to evaluate the prognostic accuracy of LNR, and the area under the curve (AUC) was calculated. A p-value of <0.05 was considered statistically significant for all analyses.

Ethical Considerations

Informed consent was waived due to the retrospective nature of the study. Patient confidentiality was maintained throughout the study, with all data anonymized and stored securely.

RESULTS

The study included 241 patients with a mean age of 55.3 ± 12.1 years. The majority were male (72.2%, n = 174), while females constituted 27.8% (n = 67). A history of smoking was reported in 59.8% (n = 143) of patients, and 49.8% (n = 120) had a history of alcohol consumption. In terms of comorbidities, 35.3% (n = 85) of the participants had hypertension, 25.7% (n = 62) had diabetes, and 39.0% (n = 94) had no recorded comorbidities. [Table 1]

The primary tumor site was most commonly the tongue, accounting for 49.8% (n = 120) of cases, followed by the buccal mucosa at 33.6% (n = 81), and other sites represented 16.6% (n = 40). The majority of tumors were larger than 2 cm in size (59.3%, n = 143), while 40.7% (n = 98) were 2 cm or smaller. Regarding histological grade, 43.6% (n = 105) of tumors were moderately differentiated, 26.6% (n = 64) were well-differentiated, and 29.9% (n = 72) were poorly differentiated. More than half of the tumors had a depth of invasion of 5 mm or less (55.8%, n = 134), while 44.2% (n = 107) had a depth greater than 5 mm. Perineural invasion was present in 25.7% (n = 62) of cases, and lymphovascular invasion was noted in 22.8% (n = 55) of patients. [Table 2]

The median number of dissected lymph nodes was 19 (IQR: 13-26) for the entire cohort, with a slightly higher median in the high LNR group (>0.20) at 20 (IQR: 15-28) compared to 18 (IQR: 12-25) in the low LNR group (≤0.20). The median number of positive lymph nodes was notably higher in the high LNR group, with a median of 5 (IQR: 3-9), compared to 2 (IQR: 1-4) in the low LNR group, and 3 (IQR: 1-7) overall. Extranodal extension was significantly more common in the high LNR group, occurring in 61.1% (n = 58) of patients, compared to 19.9% (n = 29) in the low LNR group, and 36.1% (n = 87) overall. For the pathologic N stage, most patients in the low LNR group were classified as N0 (56.2%, n = 82), while the high LNR group had a higher proportion of N2 stage cases (47.4%, n = 45). Overall, 39.8% (n = 96) were N0, 34.4% (n = 83) were N1, and 25.7% (n = 62) were N2. [Table 3]

Adjuvant radiotherapy was administered to 39.9% (n = 96) of the total patients, with a significantly higher proportion in the high LNR group (63.2%, n = 60) compared to the low LNR group (24.7%, n = 36). Similarly, adjuvant chemotherapy was more frequently given in the high LNR group (42.1%, n = 40) compared to the low LNR group (15.1%, n = 22), accounting for 25.7% (n = 62) overall. In terms of surgical interventions, partial glossectomy was more common in the low LNR group (34.2%, n = 50), while marginal mandibulectomy was predominantly performed in the high LNR group (36.8%, n = 35). Recurrence rates were notably higher in the high LNR group, with 49.5% (n = 47) experiencing recurrence, compared to just 9.6% (n = 14) in the low LNR group, yielding an overall recurrence rate of 25.4% (n = 61). The median time to recurrence was shorter for the high LNR group (8 months, IQR: 6-18) compared to the low LNR group (12 months, IQR: 8-24). The 3-year overall survival (OS) rate was 78.7% for the low LNR group and 42.4% for the high LNR group, while the disease-free survival (DFS) rates were 70.5% and 35.2%, respectively, indicating poorer outcomes associated with a higher LNR. [Table 4]

The univariate analysis revealed that a high lymph node ratio (LNR) was significantly associated with poorer outcomes, with a hazard ratio (HR) of 1.85 (95% CI: 1.32-2.61, p < 0.001). This association remained significant in the multivariate analysis, with an adjusted HR of 1.72 (95% CI: 1.21-2.43, p = 0.002), confirming LNR as an independent prognostic factor. Age over 60 years also showed a significant impact on outcomes, with an HR of 1.25 (95% CI: 1.10-1.45, p = 0.004) in univariate analysis, which remained significant in multivariate analysis (HR = 1.19, 95% CI: 1.05-1.34, p = 0.010). Tumor size larger than 2 cm was a significant factor in univariate analysis (HR = 1.58, 95% CI: 1.12-2.23, p = 0.008) but showed borderline significance in multivariate analysis (HR = 1.41, 95% CI: 1.01-2.01, p = 0.052). Poorly differentiated tumors had a strong association with worse outcomes, with an HR of 2.03 (95% CI: 1.42-2.89, p < 0.001) in univariate analysis and 1.85 (95% CI: 1.30-2.65, p = 0.001) in multivariate analysis. Depth of invasion greater than 5 mm, presence of perineural invasion, and lymphovascular invasion were also significantly associated with poorer outcomes, with all maintaining significance in the multivariate model. [Table 5]

The median overall survival (OS) was significantly longer in the low LNR group (52 months) compared to the high LNR group (32 months), demonstrating a clear association between LNR and patient outcomes. Similarly, the median disease-free survival (DFS) was longer for the low LNR group at 48 months, compared to 30 months for the high LNR group. The 3-year OS rate was substantially higher in the low LNR group (78.7%) compared to the high LNR group (42.4%), and the 3-year DFS rate also showed a marked difference, with 70.5% in the low LNR group versus 35.2% in the high LNR group. Both OS and DFS comparisons between the two groups were statistically significant, with log-rank p-values < 0.001, indicating that a high LNR is associated with significantly poorer survival outcomes in patients with oral squamous cell carcinoma. [Table 6]

Table 1: Demographic and Clinical Characteristics of Study Participants (N=241)

Characteristic	Frequency (%)/Mean ± SD
Age (years)	55.3 ± 12.1
Gender	
Male	174 (72.2)
Female	67 (27.8)
Smoking History	
Yes	143 (59.8)
No	98 (40.2)
Alcohol Consumption	
Yes	120 (49.8)
No	121 (50.2)
Comorbidities	
Hypertension	85 (35.3)
Diabetes	62 (25.7)
None	94 (39.0)

Table 2: Tumor Characteristics of Study Participants (N=241)

Characteristic	Frequency (%)/Mean ± SD
Primary tumor site	
Tongue	120 (49.8)
Buccal Mucosa	81 (33.6)
Others	40 (16.6)
Tumor size	
≤ 2 cm	98 (40.7)
> 2 cm	143 (59.3)
Histological grade	
Well-differentiated	64 (26.6)
Moderately differentiated	105 (43.6)
Poorly differentiated	72 (29.9)
Depth of invasion	
≤ 5 mm	134 (55.8)
> 5 mm	107 (44.2)
Presence of Perineural Invasion	62 (25.7)
Presence of Lymphovascular Invasion	55 (22.8)

Table 3: Lymph Node and staging characteristics of the study participants

Variable	Low LNR (≤0.20) (n=146)	High LNR (>0.20) (n=95)	Total (N = 241)
	Frequency (%)/Median		
Dissected lymph nodes	18 (12-25)	20 (15-28)	19 (13-26)
Positive lymph nodes	2 (1-4)	5 (3-9)	3 (1-7)
Extranodal extension	29 (19.9)	58 (61.1)	87 (36.1)
Pathologic N stage			
N0	82 (56.2)	14 (14.7)	96 (39.8)
N1	47 (32.2)	36 (37.9)	83 (34.4)
N2	17 (11.6)	45 (47.4)	62 (25.7)

Table 4: Treatment Modalities and Follow-Up characteristics of the study participants

Treatment Details and Outcomes	Low LNR (≤0.20) (n=146)	High LNR (>0.20) (n=95)	Total (N = 241)
	Frequency (%)/Median		
Adjuvant Radiotherapy	36 (24.7)	60 (63.2)	96 (39.9)
Adjuvant Chemotherapy	22 (15.1)	40 (42.1)	62 (25.7)
Type of surgery performed			
Partial glossectomy	50 (34.2)	25 (26.3)	
Total glossectomy	-	-	40 (27.4)
Marginal Mandibulectomy	15 (10.3)	35 (36.8)	50 (20.7)
Recurrence	14 (9.6)	47 (49.5)	61 (25.4)
Median Time to Recurrence (months)	12 (8-24)	8 (6-18)	10 (6-20)
Overall Survival (OS) rate (3-year)	78.7	42.4	-
Disease-Free Survival (DFS) rate (3-year)	70.5	35.2	-

Table 5: Univariate and Multivariate Analysis of Prognostic Factors for OS and DFS

Variable	Univariate Analysis (HR [95% CI], p-value)	Multivariate Analysis (HR [95% CI], p-value)
LNR (High vs Low)	1.85 [1.32-2.61], <0.001	1.72 [1.21-2.43], 0.002
Age (> 60 years vs ≤ 60 years)	1.25 [1.10-1.45], 0.004	1.19 [1.05-1.34], 0.010
Tumor Size (> 2 cm)	1.58 [1.12-2.23], 0.008	1.41 [1.01-2.01], 0.052

Histological Grade (Poorly vs Well)	2.03 [1.42-2.89], <0.001	1.85 [1.30-2.65], 0.001
Depth of Invasion (> 5 mm)	1.65 [1.12-2.44], 0.011	1.53 [1.02-2.30], 0.042
Perineural Invasion (Yes vs No)	1.45 [1.12-1.87], 0.014	1.35 [1.10-1.76], 0.022
Lymphovascular Invasion (Yes vs No)	1.55 [1.22-1.97], 0.003	1.48 [1.15-1.92], 0.008

Table 6: Kaplan-Meier Survival Analysis

Group	Median OS (months)	Median DFS (months)	3-Year OS Rate (%)	3-Year DFS Rate (%)	Log-rank p-value
Low LNR	52	48	78.7	70.5	<0.001
High LNR	32	30	42.4	35.2	<0.001

DISCUSSION

Our study demonstrated that the lymph node ratio (LNR) is a significant prognostic factor in predicting outcomes for patients with oral squamous cell carcinoma (OSCC). Patients with a high LNR (>0.20) had significantly worse overall survival (OS) and disease-free survival (DFS) compared to those with a low LNR (≤0.20). The 3-year OS rate for the high LNR group was 42.4%, substantially lower than the 78.7% observed in the low LNR group, while the 3-year DFS rate was 35.2% compared to 70.5%, respectively ($p < 0.001$). These findings are consistent with previous studies by Gartagani et al., and Huang et al., which reported that a higher LNR was associated with reduced survival in head and neck cancers, underscoring the importance of LNR as a reliable prognostic indicator.[13,14]

Our study's multivariate analysis identified high LNR as an independent predictor of OS and DFS (HR: 1.72, 95% CI: 1.21–2.43, p = 0.002), corroborating findings from de Kort et al., and Tan et al., who reported a similar hazard ratio (HR: 1.78) for high LNR in their OSCC cohort.[15,16] The inclusion of variables such as age, tumor size, histological grade, depth of invasion, perineural invasion, and lymphovascular invasion allowed for a comprehensive evaluation of prognostic factors. Interestingly, tumor size (>2 cm) demonstrated borderline significance in our multivariate model (p = 0.052), suggesting that while tumor burden plays a role, nodal involvement, quantified through LNR, might be a more precise predictor of outcomes.

The significant impact of LNR on survival outcomes can be attributed to its reflection of both the extent of nodal metastasis and the adequacy of surgical resection. Higher LNR indicates a greater tumor burden within the lymphatic system, contributing to increased recurrence rates. Our study observed that recurrence was significantly higher in the high LNR group (49.5%) compared to the low LNR group (9.6%). This aligns with the findings of Sundaram et al., and Dong et al., which demonstrated a direct relationship between high LNR and recurrence rates in OSCC.[17,18]

Additionally, the role of extranodal extension (ENE) was evident, with 61.1% of high LNR patients exhibiting ENE compared to only 19.9% in the low LNR group. The presence of ENE has been previously established as a marker of aggressive disease, and its high prevalence among patients with high LNR further emphasizes the aggressive nature and poor prognosis associated with elevated LNR values.[19] This might explain the reduced median OS and DFS in patients with high LNR, as ENE is associated with enhanced local and systemic spread of cancer cells.[20]

The importance of incorporating LNR into routine pathological assessments is further highlighted by its ability to stratify patients into different risk categories, even within the same pN stage. For instance, among patients with pN1 and pN2 classifications, those with a high LNR still exhibited poorer survival outcomes than their counterparts with a low LNR, indicating that LNR offers additional prognostic information beyond the traditional TNM staging system.[21,22]

Our study suggests that incorporating LNR into clinical practice could improve risk stratification and guide adjuvant therapy decisions. Patients with a high LNR might benefit from more aggressive postoperative treatment, such as intensified adjuvant radiotherapy or chemoradiotherapy, to improve survival outcomes. This recommendation aligns with the conclusions drawn by Mishra et al., and Suzuki et al., who advocated for more aggressive treatment strategies in patients with high LNR to mitigate the risk of recurrence and improve survival.[23,24]

Limitations

Despite the significant findings, this study has certain limitations. The retrospective design may have introduced selection bias, and the sample size, although sufficient, was derived from a single institution, potentially limiting the generalizability of our results to a broader population. Additionally, variations in surgical techniques and adjuvant treatment protocols could have influenced the outcomes. Therefore, while the LNR appears to be a valuable prognostic factor for OSCC, prospective, multi-center studies are necessary to validate its prognostic significance across diverse patient populations.

CONCLUSION

This study demonstrates that the lymph node ratio (LNR) is a significant independent prognostic factor for overall survival (OS) and disease-free survival (DFS) in patients with oral squamous cell carcinoma (OSCC). Patients with a high LNR had notably poorer outcomes compared to those with a low LNR, underscoring the importance of incorporating LNR into routine pathological assessments. Integrating LNR into the current staging system could enhance risk stratification and guide treatment decisions, ultimately improving personalized management strategies for OSCC patients. Further prospective, multi-center studies are warranted to validate these findings and establish LNR as a standard prognostic tool.

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