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ORIGINAL RESEARCH

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Prognostic value of pretreatment lymphocyte-to-monocyte ratio in patients with advanced oral cavity cancer

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Abstract

Introduction: Lymphocyte-to-monocyte ratio (LMR) has been reported as a prognostic factor in many cancers but the data are to date limited for its use in oral cavity cancer. The purpose of this study was to evaluate the prognostic value of LMR in advanced-stage oral cavity cancer.

Methods: Data from 211 advanced-stage oral cancer patients treated with curative intent between January 2009 and December 2015 were obtained from the hospital information system. Pretreatment LMR and other hematologic parameters were recorded and an LMR cutoff value was calculated. Overall survival between the groups above (high LMR) and below (low LMR) the cutoff was compared and hazard ratios from univariate and multivariate analyses using a Cox proportional hazards model calculated.

Results: Overall survival and disease-specific survival were better in the high LMR group. The 5-year overall survival rates were 31.6% and 15% in the high LMR and low LMR groups, respectively. Multivariate analysis using a Cox proportional hazards model showed that treatment modality and LMR were the only factors associated with overall survival.

Conclusion: Low LMR was associated with poor survival outcome in patients with advanced-stage oral cavity cancer.

Level of Evidence: 2b.

KEYWORDS
lymphocyte-to-monocyte ratio, oral squamous cell carcinoma, prognosis

1 | INTRODUCTION

Cancer of the oral cavity is one of the most common head and neck cancers. The age-standardized rates (ASR) for this cancer reported by the US National Cancer Institute in 2015 were 11 per 100,000 persons and 2.5 deaths per 100,000 persons.[1] The most recent ASR rate (2014) in Songkhla, a province in southern Thailand, for oral cavity cancer was 7.3 per 100,000 persons.[2] One study reported that localized oral cavity cancer had 5-year overall survival rates of 60–70%, but these decreased by 50% when there was nodal involvement.[3] When comparing treatments begun in early-stage vs advanced-stage cancers, the survival rate decreased from 74% to 33%.[4] The mortality rate of oral cavity cancers is

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influenced by many factors such as smoking, alcohol drinking, use of smokeless tobacco, initial staging and treatment modality.[5,6] However, there are also varying treatment outcomes among patients with the same staging and treatments, indicating other factors are involved, such as differences in the biological activity of the tumor.

Many recent studies have investigated inflammatory cells in the peripheral blood that are associated with tumor growth and treatment outcomes. One study reported that lymphocytes played an important role in the tumor microenvironment and in inhibiting tumor growth.[7] Another study found that lower levels of lymphocytes were related to poorer treatment outcomes.[8] In addition to lymphocytes, other studies have found that monocytes promoted tumor proliferation by producing pro-inflammatory cytokines and promoting tumor angiogenesis.[9,10] Many studies have investigated the prognostic value of the lymphocyte-to-monocyte ratio (LMR) in various solid tumors such as hepatocellular carcinoma, lung cancer, cervical cancer, esophageal cancer, and head and neck cancers including nasopharynx, oropharynx, larynx and hypopharynx and found that lower LMRs were related to poorer survival outcomes.[11–19] The mainstay treatment of oral cavity cancer is surgery, which is different from other head and neck cancers that rely more on radiation. The prognostic value of LMR in cancers varies depending on tumor location but its utility in the assessment of oral cavity cancer has not yet been established, especially in advanced-stage oral cavity cancer which has poorer overall survival compared to early-stage cancer. In the present study, the main objective was to evaluate the prognostic value of LMR in advanced-stage oral cavity cancer.

2 | MATERIALS AND METHODS

2.1 | Patient selection

This retrospective study enrolled 211 patients from the cancer registry database of Prince of Songkla University Hospital from January 2009 to December 2015. The inclusion criteria were previously untreated stage III or IV squamous cell carcinoma of the oral cavity and treatment with curative intent. Patients with distant metastases, other malignancies, autoimmune disease, renal failure, hematologic disease and/or use of immunosuppressant medications were excluded from the study. Ethical approval was given by the institutional review board. Informed consent was waived in this retrospective study.

2.2 | Data collection

All data from the records of patients with stage III or IV squamous cell carcinoma of the oral cavity during the study period were extracted from the data base. Cancer staging was based on the American Joint Commission on Cancer Staging Manual of the time each patient was assessed. Pretreatment hematologic parameters were collected within 1 month before initial treatment. Other information collected included demographic characteristics, tumor subsite, TNM staging and primary treatment, with a follow up time of at least 1 year after initial treatment or when the patient died.

2.3 | Statistical analysis

Descriptive data are shown as frequency, percentage or mean with standard deviation. A receiver operating characteristic (ROC) curve was plotted to evaluate the predictive ability of pretreatment LMR. The cutoff value was derived from the maximum value of Youden's index (*J*) which identifies the point that yields the highest sensitivity plus specificity minus one on an ROC curve.[20] The index values range from 0 to 1. The cutoff value calculated from this method provides the best tradeoff between sensitivity and specificity to maximize the effectiveness of a diagnostic biomarker. This index gives equal weight to false positive and false negative values. The Chi-square test was used to examine relationships between clinical characteristics and LMR. Overall survival and disease-specific survival were plotted using the Kaplan–Meier method and the log-rank tests were used to identify differences in overall survival rates. A Cox proportional hazards model was used to identify the effect of each factor on

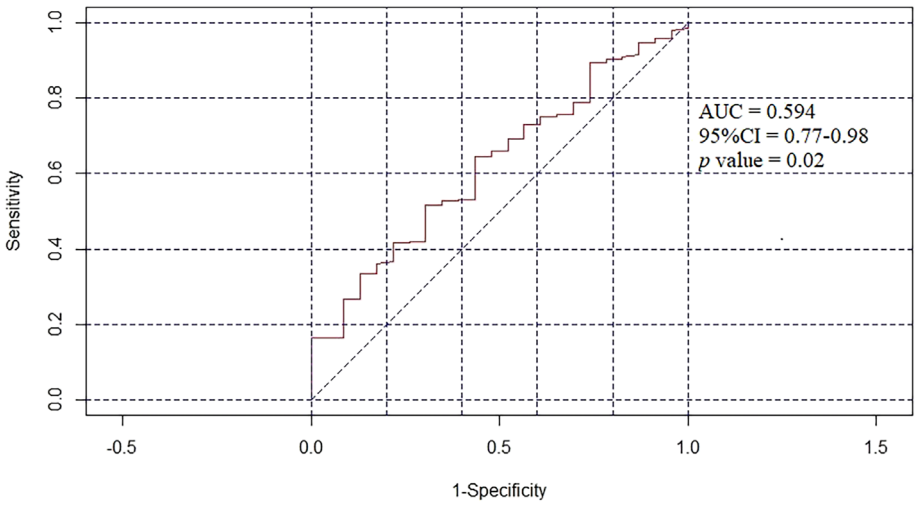

FIGURE 1 ROC curve to identify optimal cutoff value for lymphocyte-to-monocyte ratio

overall survival. All statistical analyses were done with the R program version 1.3.1073.

3 | RESULTS

3.1 | Optimal cutoff value for lymphocyte-to-monocyte ratio

An ROC curve was plotted as shown in Figure 1 to ascertain the best cutoff value from Youden's index analysis for a lymphocyte-to-monocyte ratio. The area under the curve for this LMR was 0.594 with specificity and sensitivity of 0.570 and 0.614, respectively. The optimal cutoff value which yielded the highest sensitivity plus specificity was 4. The patients were then divided into two groups for analysis, the first group with LMR < 4 had 95 patients, the other group with LMR ≥ 4 had 116 patients.

TABLE 1 Baseline characteristics of the study groups

	LMR <4, *n* (%)	LMR ≥4, *n* (%)	*p* value
Age			.378
<60	55 (57.9)	59 (50.9)	
>60	40 (42.1)	57 (49.1)	
Gender			.576
Female	30 (31.6)	42 (36.2)	
Male	65 (68.4)	74 (63.8)	
Subsite			.425
Buccal mucosa	7 (7.4)	16 (13.8)	
Floor of mouth	14 (14.7)	23 (19.8)	
Gingiva	22 (23.2)	20 (17.2)	
Hard palate	4 (4.2)	5 (4.3)	
Lip	1 (1.1)	2 (1.7)	
Oral tongue	38 (40)	45 (38.8)	
Retromolar trigone	9 (9.5)	5 (4.3)	
T stage			.307
T1	1 (1.1)	3 (2.6)	
T2	16 (16.8)	15 (12.9)	
T3	9 (9.5)	21 (18.1)	
T4a	60 (63.2)	70 (60.3)	
T4b	9 (9.5)	7 (6)	
N stage			.447
N0	21 (22.1)	38 (32.8)	
N1	25 (26.3)	21 (18.1)	
N2a	5 (5.3)	4 (3.4)	
N2b	21 (22.1)	28 (24.1)	
N2c	19 (20)	22 (19)	
N3	4 (4.2)	3 (2.6)	
Stage			.173
III	12 (12.6)	24 (20.7)	
IV	83 (87.4)	92 (79.3)	
Treatment			.692
CCRT	37 (38.9)	41 (35.3)	
Surgery	58 (61.1)	75 (64.7)	
With PORT	39 (41.1)	59 (50.9)	
With POCCRT	19 (20)	16 (13.8)	

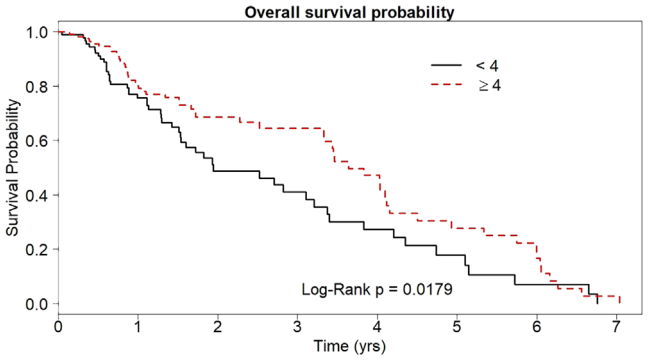

FIGURE 2 Kaplan–Meier plots of overall survival of the study oral cavity cancer patients comparing LMR < 4 and LMR ≥ 4

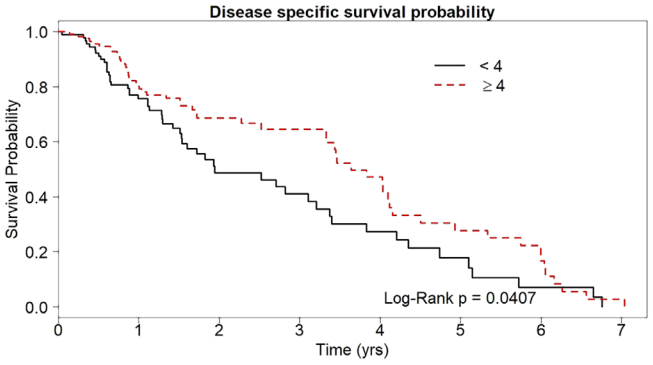

FIGURE 3 Kaplan–Meier plots of the disease-specific survival of the study oral cavity cancer patients comparing LMR < 4 and LMR ≥ 4

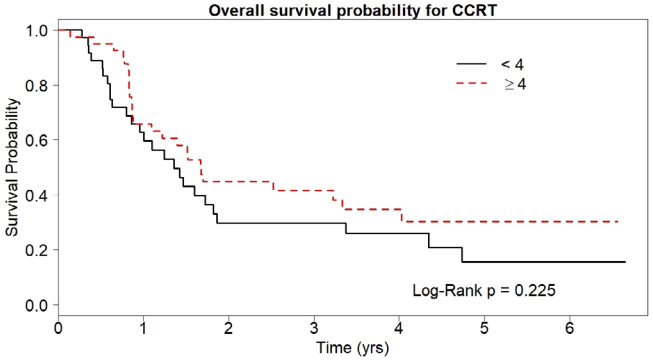

FIGURE 4 Kaplan–Meier plots of the overall survival of the study oral cavity cancer patients treated with CCRT comparing LMR <4 and LMR ≥ 4

3.2 | Patient characteristics

Two hundred and eleven patients with advanced-stage oral cavity cancer were enrolled in the study, 139 (65.9%) male and 72 (34.1%) female with mean (SD) ages of 59.1 (12.3) and 59.4 (13.9), respectively. The most common tumor subsite was the oral tongue which accounted for 39.3% of the tumors. 78 (37%) patients were treated with CCRT and 133 (63%) patients were treated with either surgery with postoperative radiation (PORT) or surgery with postoperative concurrent chemoradiation (POCCRT), depending on the pathological status of the patient.

There were no statistically significant differences between the two groups in all major baseline categories as shown in Table 1.

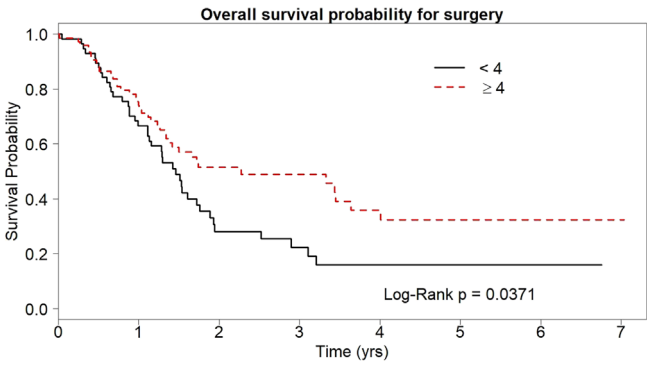

FIGURE 5 Kaplan–Meier plots of the overall survival of the study oral cavity cancer patients treated with surgery comparing LMR < 4 and LMR ≥ 4

3.3 | Survival outcome

Overall survival and "disease specific" survival were better in the high LMR group as shown in the Kaplan–Meier survival curves shown in Figures 2 and 3. The 5-year overall survival rates were 15% and 31.6% in the low LMR group and high LMR group, respectively. The 5-year "disease specific" survival rates were 17.7% and 27.8% in the low LMR and high LMR groups, respectively.

Subgroup analyses were performed for the surgery and CCRT groups. The overall survival rates for the CCRT group were not statistically significantly different between the high and low LMR groups but overall survival in the surgery group was better in the high LMR group compared to the low LMR group as shown in Figures 4 and 5.

TABLE 2 Univariate and multivariate analyses results

Characteristic	Univariate HR (95% CI)	*p* value	Multivariate HR (95% CI)	*p* value
Age group (years)		.098		.036
<60	1 (reference)		1 (reference)	
>60	1.34 (0.95,1.89)		1.36 (0.96,1.93)	
Gender		.512		ND
Female	1 (reference)			
Male	0.89 (0.62,1.27)			
Tumor subsite		.857		ND
Buccal mucosa	1 (reference)			
Floor of mouth	0.87 (0.45,1.68)			
Gingiva	1.07 (0.56,2.01)			
Hard palate	1.06 (0.38,2.92)			
Lower lip	0.48 (0.06,3.66)			
Oral tongue	1.13 (0.64,2.01)			
Retromolar trigone	1.38 (0.6,3.17)			
Stage		.602		.441
III	1 (reference)		1 (reference)	
IV	0.89 (0.57,1.38)		0.83 (0.53,1.31)	
Treatment		.005		.001
Surgery with free margin	1 (reference)		1 (reference)	
Surgery but not free margin	1.73 (1.06,2.8)		2 (1.21,3.29)	
CCRT	1.81 (1.24,2.66)		1.98 (1.31,2.98)	
LMR		.019		.037
≥4	1 (reference)		1 (reference)	
<4	1.51 (1.07,2.12)		1.44 (1.02,2.04)	

3.4 | Survival analysis

Univariate and multivariate analyses using Cox proportional hazards models showed that treatment modality and LMR were associated with overall survival while age, gender, tumor subsite and stage were not, as shown in Table 2.

4 | DISCUSSION

This study aimed to evaluate the prognostic value of the LMR in patients with advanced- stage oral cavity cancer. Treatment modality and LMR were found to be significant prognostic factors for overall survival. Various studies have reported that treatment modality affected the survival rates of head and neck surgery patients but this study also found that LMR was another independent prognostic factor for advanced-stage oral cavity cancer. After adjustment for confounding factors, the multivariate Cox proportional hazards model also showed the same results with hazard rates of 2.3 and 1.48.

Many studies have investigated the value of the LMR as a prognostic factor for various cancers. Kano et al. reported the prognostic values of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and lymphocyte-to-monocyte ratio in head and neck cancers treated with concurrent chemoradiation including hypopharyngeal, laryngeal and oropharyngeal cancers. Their study found that only the LMR was an independent prognostic factor.[13]

In the current study, more than 60 percent of the patients were treated with surgery and LMR was also associated with overall survival in these patients, but not in patients who were treated with CCRT. This finding might be due to the fact that most patients in the CCRT group had poor overall survival due to advanced-stage, unresectable disease and/or other comorbidities that made them ineligible for surgery. In 2015, Nishijima et al. did a systematic review and meta-analysis in non-hematologic malignancies such as lung cancer, breast cancer, esophageal cancer, nasopharyngeal cancer and others, and found that a low LMR was related to poor survival outcomes.[16]

As noted in the Nishijima meta-analysis, many cutoff values have been used to divide patients between high and low LMR groups, ranging from 2 to 5.26. One study reported that the hazard ratios of LMR were 1.73 with 95% CI 1.55–1.93.[16] The current study used a cutoff value of 4 derived from a Youden's index analysis. This method has the main advantage over most other methods of balancing between false positive and false negative values to maximize the effectiveness of diagnostic biomarkers and this method has been used by many studies to acquire optimal cutoff values.[11,13,15] One study reported the cutoff value of 4.29 for LMR in tongue cancer,[21] which was higher than the cutoff value in the current study. These different results may be due to a relatively decreased number of lymphocytes and increased monocytes related to the advanced-stage disease patients in our study, that resulted in a low LMR.[13] Using this cutoff, the low LMR group had overall worse survival than the high LMR group in patients with advanced-stage oral cavity cancer. The hazard ratio for low LMR in this study was 1.44 with a 95% CI 1.02–2.04, which was less than the hazard ratio found in the meta-analysis.

Based on this study's findings and earlier studies, there appears to be a significant association between LMR and survival outcome in advanced-stage oral cancer patients. The tumor microenvironment is known be an important factor influencing tumor progression or suppression. Tumor-infiltrating lymphocytes (TILs) play a major anti-tumor role by activation of cellular and humoral immune responses. Various studies have reported that a low number of TILs was associated with poor survival outcomes.[7,9,17,22] Tumor-associated macrophages (TAMs), which are derived from circulating monocytes, accelerate tumor growth by producing pro-inflammatory cytokines and promoting tumor angiogenesis.[10] High TAMs have been associated with poor prognoses,[23] so it seems possible that the LMR may reflect the host immune system in the tumor microenvironment which could suppress or accelerate tumor progression.

The study had some limitations. First, it was a retrospective study so the possibility of selection bias was unavoidable. Second, the sample size was low because this was a single-center study examining a relatively uncommon disease. Third, this study could not elucidate a relationship between circulating monocytes and TAMs due to a problem in obtaining tissue specimens for immunohistochemistry. Further prospective studies with larger sample sizes including tissue specimens to analyze the relationship between circulating monocytes and TAMs are needed.

5 | CONCLUSION

A low LMR was associated with poor survival outcome in patients with advanced-stage oral cavity cancer, especially in patients who had surgical treatment.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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