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ORIGINAL RESEARCH

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Prognostic value of absolute lymphocyte count in oral cavity squamous cell carcinoma

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Abstract

Objective(s): Absolute lymphocyte count (ALC) has been shown to be a prognostic indicator in other solid tumors. Given this, we aimed to evaluate the prognostic value of ALC in oral cavity squamous cell carcinoma (OSCC).

Methods: Using our institutional tumor registry data, we identified patients ≥18 years old who were diagnosed with OSCC between 2012 and 2018. Preoperative ALC values within 30 days of surgery were collected through retrospective chart review. American Joint Committee on Cancer, 7th-edition best stage was used to categorize cancers as early stage (stages 1 and 2) or late-stage (stages 3 and 4). Primary outcomes were likelihood of recurrence and survival rates after 3 years.

Results: Of the 412 patients identified, 262 patients had available ALC data and met inclusion criteria. Early stage cancer patients who had lymphopenia did not have any significant difference in their rate of death ([OR], 1.71, CI: 0.54–5.45, $p = .36$) or likelihood recurrence ([OR], 0.60, CI: 0.06–5.87, $p = .66$) after controlling for age, tobacco use, alcohol use, positive margins, and adjuvant therapy. Late-stage cancer patients who had lymphopenia also showed no difference in their rate of death ([OR], 2.74, CI: 0.65–11.6, $p = .17$) or likelihood of recurrence ([OR], 0.38, CI: 0.04–3.36, $p = .38$).

Conclusions and Relevance: This study evaluates the prognostic value of ALC in oral cavity cancers. Our findings demonstrate that pretreatment ALC is not significantly associated with recurrence and survival outcomes patients with OSCC.

Level of Evidence: III

Lay Summary: Absolute lymphocyte count (ALC) has been associated with prognosis in several cancers. We found that preoperative ALC was not associated with likelihood of survival or recurrence in patients with early stage or late-stage oral cavity cancer.

KEYWORDS

lymphocyte, oral cavity, prognosis, squamous cell carcinoma, survival

This study has been deemed exempt by the Yale University Institutional Review Board (IRB Protocol ID# 2000034103).

1 | INTRODUCTION

Cancers of the oral cavity are associated with a high mortality rate and are the eleventh most common cancer worldwide.[1] In fact, the 5-years survival rate of oral and pharyngeal cancers in the United States has remained comparatively low around 67%, in contrast to the 5-years survival rates of 90% for breast cancer and 98% for prostate cancer.[2] Using noninvasive and readily available biomarkers as prognostic indicators may help improve outcomes without increasing the burden on patients or the healthcare system by allowing clinicians to identify high-risk oral cavity squamous cell carcinoma (OSCC) patients who may benefit from earlier aggressive therapies.

One candidate biomarker is absolute lymphocyte count (ALC), which is a routinely obtained marker that has been investigated as a prognostic indicator in multiple cancer types.[3,4] ALC can provide a surrogate measure of the host's inflammatory and immune responses given the critical role of lymphocytes in the tumor-related immune response.[5] A number of studies have shown an association between lymphopenia and poor prognosis in cancers such as sarcoma, breast cancer, renal cancer, and gastric cancer.[4,6–9]

However, the existing data on the reliability of ALC as a prognostic biomarker is mixed, with some studies showing inconsistent results regarding pretreatment lymphocyte counts. For instance, Punjabi et al. showed no significant correlation between pretreatment ALC and survival outcomes in nonsmall cell lung cancer, although there was an association between postradiotherapy ALC and survival outcomes.[10] These findings were consistent with a meta-analysis, which demonstrated no significant correlation between pretreatment ALC and overall survival in five studies of lung cancer.[4]

Furthermore, there is limited data regarding the utility of ALC as a biomarker in head and neck cancers. The majority of studies focus on nasopharyngeal cancers and show mixed results regarding pretreatment peripheral blood counts; two studies found no significant association between lymphocyte counts and overall survival, although other measures such as neutrophil–lymphocyte ratio (NLR) demonstrated prognostic value for survival outcomes.[11–13] It is therefore critical to investigate the strength of ALC as a biomarker in specific cancer types to validate its utility in clinical practice.

In this study, we aim to assess the prognostic value of ALC in oral cavity cancer using preoperative ALC measurements from patients who received treatment at our institution between 2012 and 2018.

2 | MATERIALS AND METHODS

2.1 | Study population

Patients ≥18 years old diagnosed with OSCC between January 2012 to December 2018 and who underwent all treatment at Yale-New Haven Hospital were identified from the hospital tumor registry. Primary sites and histology characterized by International Classification of Disease for Oncology, third edition (ICD-O-3) were used to identify patients with squamous cell carcinomas (ICD-O-3 histology codes 8070–8076) of the tongue (C020-C023, C028-C029), floor of mouth (C040, C041, C048, C049), gums (C030, C031, C039), palate (C050, C058, C059), and other parts of oral cavity (C060-C062, C068, C069). Patients were excluded if they: (1) did not undergo surgery; (2) received surgery or radiation outside the state; (3) treatment location for surgery or radiation was unknown. All patients included were those that presented for the first time for an oral cancer isolated malignancy. All patients underwent primary surgery. This study was deemed exempt by the Institutional Review Board of Yale University.

2.2 | Predictor and outcome variables

Primary outcome measures were death and recurrence rates after 3 years. All patients in our study had 3-years survival and recurrence data. The predictor variable investigated was ALC. ALC values were collected preoperatively, within 30 days of surgery, and the most recent value within that timeframe was recorded. Patients without ALC values were excluded from analysis.

2.3 | Additional data collected

Demographic variables were obtained from tumor registries: age at diagnosis, sex, race, insurance status, alcohol, and tobacco-use. Cancer-related and treatment variables were obtained from the tumor registry and verified through medical records review such as primary site, margin status, receipt of adjuvant therapy, and American Joint Committee on Cancer (AJCC) seventh-edition best stage. AJCC stages 1 and 2 were categorized as early stage and stages 3 and 4 as late stage.

2.4 | Statistical analysis

Statistical analyses were performed in SPSS Statistics v.28 (Armonk, NY). Binary logistic regressions and two-sided Fisher's exact test were each, respectively, used to analyze ALC continuously and ever-lymphopenia categorically against both death and recurrence. Our models included two-tailed student *t*-tests were used to compare mean ALC values between early stage and late stage OSCC. For categorical comparisons, patients were divided into ever-lymphopenia and never-lymphopenia with lymphopenia being categorized as <1000/μL. The *p*-values ≤.05 were considered statistically significant.

For assessment of covariates used in the multivariate analysis, binary logistic regression was used for continuous variables (i.e., age) against death and recurrence and two-sided Fisher Exact Test was used for categorical variables (i.e., tobacco use, alcohol use, positive margin presence, and use of adjuvant therapy). Covariates were selected on the basis of their nature as risk factors for oral cancer and

TABLE 1 Patient cohort characteristics.

Factors	Total ($n = 262$)
Age (years), (mean ± SD)	63.8 ± 14.0
Preoperative absolute lymphocyte count (mean ± SD)	1.8 ± 0.76
Insurance status, % (*n*)	
Not insured	3.1 (8)
Private	38.2 (100)
Government insurance	58.7 (154)
Male sex, % (*n*)	58.0 (152)
Race-white, % (*n*)	85.5 (224)
Smoking-ever, % (*n*)	67.4 (177)
Alcohol-ever, % (*n*)	66.4 (174)
Primary site, % (*n*)	57.0 (235)
Tongue	59.2 (155)
Floor of mouth	13.0 (34)
Hard palate	2.3 (6)
Gum	11.8 (31)
Other	13.7 (36)
Positive margins, % (*n*)	5 (1.9)
Adjuvant therapy, % (*n*)	50 (131)
Tumor stage, % (*n*)	
Early	50.8 (133)
Late	49.2 (129)
Recurrence—yes, % (*n*) (3 years)	18.3 (48)
Death—yes, % (*n*) (3 years)	35.9 (94)

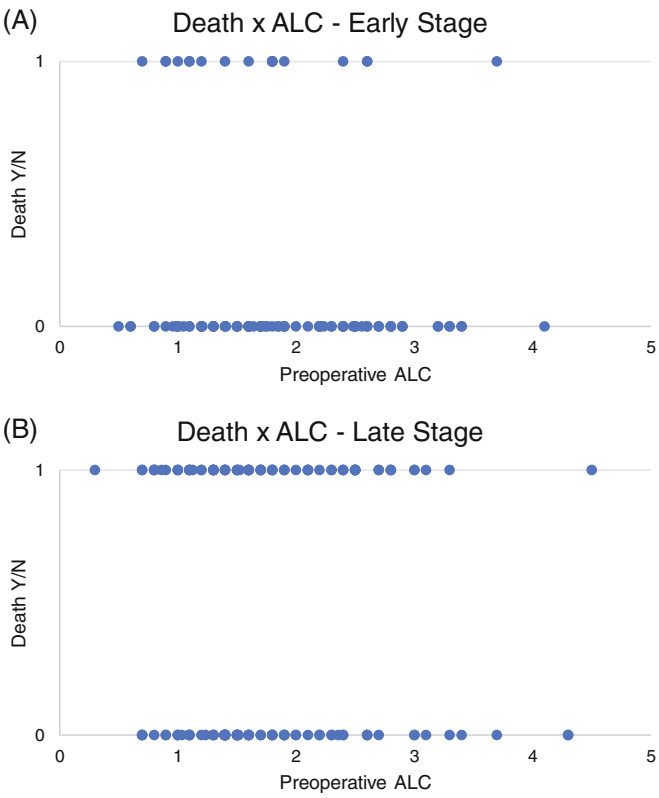

FIGURE 1 (A) The relationship between preoperative absolute lymphocyte count (ALC) and incidence of recurrence with 1 = yes and 0 = no when looking at patients with early stage oral cavity squamous cell carcinoma (OSCC). (B) The relationship between preoperative ALC and incidence of recurrence with 1 = yes and 0 = no when looking at patients with late stage OSCC.

their ability to impact a patient's likelihood for recurrence and survival.

Multivariate logistic regressions assessed the relationship between lymphopenia in early and late-stage cancer (the independent variable) and death/recurrence (the dependent variables), while controlling for age, tobacco use, alcohol use, positive margin presence, and use of adjuvant therapy.

3 | RESULTS

3.1 | Cohort characteristics

Of the 412 patients that were diagnosed with OSCC at our institution between 2012 and 2018, 262 patients had ALC data and met the inclusion criteria for our final cohort. The median age at diagnosis was 63.8 +/−14.0 years and 58.0% of our population was male. Additional demographic data is presented in Table 1. The median ALC value for our cohort was 1.8 +/−0.76. Twenty five patients (9.5%) in our cohort had ever-lymphopenia, 133 patients were in the late-stage cohort and 129 patients were in the early stage cohort. Within the early stage cohort, 15 (11.4%) had ever-lymphopenia. Within the late-stage cohort, 10 (7.8%) had ever-lymphopenia. The overall rate of death was 35.9% and the overall rate of recurrence was 18.3%. Within the early-stage cohort, 13 (9.8%) patients recurred, and 87 (65.4%) patients died. Within the late-stage cohort, 35 (27.1%) patients recurred, and 81 (62.8%) patients died.

The primary site breakdown is 59.2% tongue, 13% floor of mouth, 11.8% gum, 2.3% hard palate, and 13.7% other (Table 1). The histology of the tumors for all patients was squamous cell carcinoma; 1.9% of patients of had positive margins. 50% of the cohort had some sort of adjuvant therapy (50% received radiation and 17.9% of those also received chemotherapy).

3.2 | Association of ALC with death and recurrence

ALC values ranged from 300/μL to 4500/μL. When analyzing ALC continuously, there was no impact on incidence of recurrence ([OR], 1.35, CI: 0.91–2.01, $p = .13$) or death ([OR], 0.87, CI: 0.67–1.22, $p = .40$). When looking at ever-lymphopenia categorically, there was no association with incidence of recurrence ($p = .27$) or death ($p = .20$). When stratifying the data by early stage and late

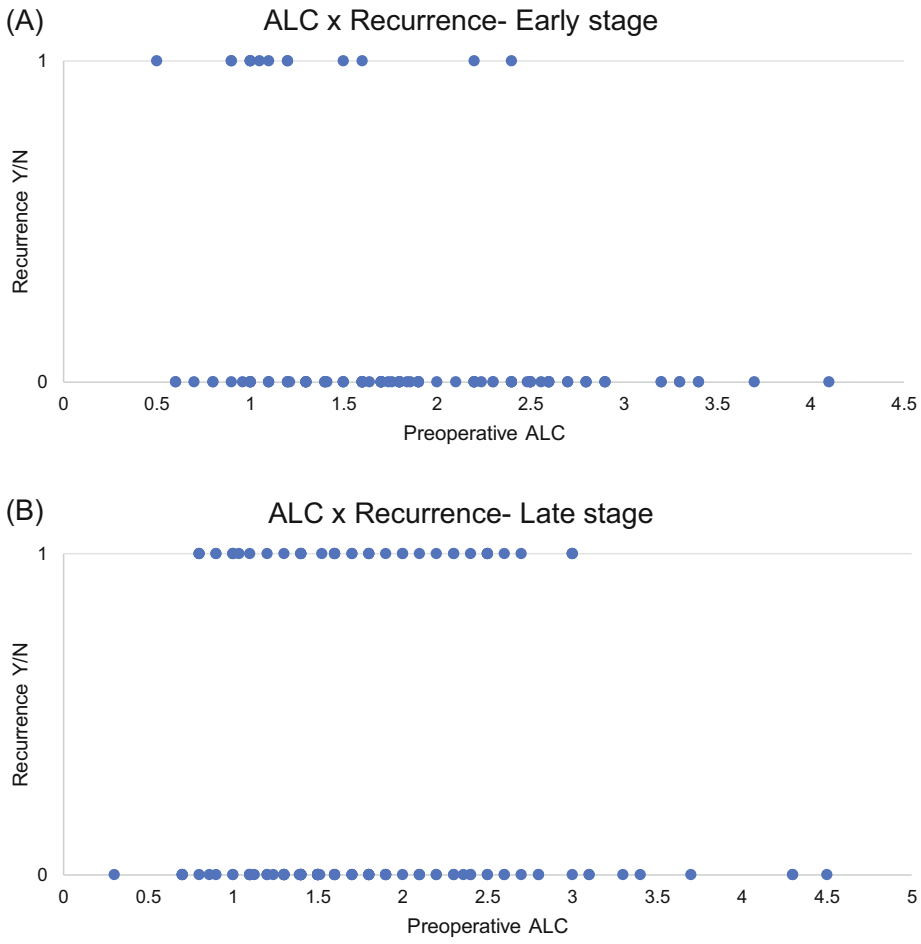

FIGURE 2 (A) The relationship between preoperative absolute lymphocyte count (ALC) and incidence of death with 1 = yes and 0 = no when looking at patients with early stage oral cavity squamous cell carcinoma (OSCC). (B) The relationship between preoperative ALC and incidence of death with 1 = yes and 0 = no when looking at patients with late stage OSCC.

stage AJCC seventh edition final stage, the mean ALC values for early stage vs. late stage OSCC was 1.84 and 1.78, respectively ($p = .53$).

When analyzing the significance of the covariates against the outcome variables of death, age ([OR], 0.99, CI: 0.97–1.00, $p = .3$), tobacco history ($p = .89$), and positive margins ($p = .06$) were not significant. The covariates of adjuvant therapy ($p = .05$) and alcohol history ($p = .03$) were significantly associated with death. When analyzing the covariates against the outcome variable of recurrence, age ([OR], 1.0, CI: 0.98–1.02, $p = .91$), tobacco history ($p = .61$), adjuvant therapy ($p = .42$), and positive margins ($p = .24$) were not significant. The covariate of alcohol history ($p = .003$) was significantly associated with recurrence.

Patients were then grouped categorially into ever-lymphopenia and never-lymphopenia and stratified by early and late-stage cancer. On multivariate analysis, patients with early stage OSCC who had lymphopenia did not have any significant difference in their rate of death ([OR], 1.71, CI: 0.54–5.45, $p = .36$) or recurrence ([OR], 0.60, CI: 0.06–5.87, $p = .66$) after controlling for age, tobacco use, alcohol use, positive margins, and use of adjuvant therapy. Multivariate analysis with the same parameters for late-stage OSCC patients also showed no difference in rates of death ([OR], 2.74, CI: 0.65–11.6, $p = .17$) or recurrence ([OR], 0.38, CI: 0.04–3.36, $p = .38$) in patients who had lymphopenia.

4 | DISCUSSION

Given the relatively poor five-years survival rates of head and neck cancer patients, there has been increasing emphasis on investigating the predictive ability of different biomarkers, specifically inflammatory and hematologic in an effort to develop targeted treatments and improve patient counseling.[14] Previous studies specifically in oral cavity cancer patients have found that high pretreatment circulating monocyte counts and NLR are markers for poor disease-specific survival.[15–17] The studies looking at predictivity of ALC in head and neck have been more discordant. When looking at oropharyngeal cancer, lower pretreatment ALC was prognostic for worse overall survival, but studies in nasopharyngeal carcinoma (NPC) showed that pretreatment ALC was not predictive marker for survival.[12,13,18] However, the NPC studies did show that treatment-related lymphopenia, high NLR, and high platelet lymphocyte ratio (PLR) was associated with worse survival.[12,13]

This study evaluates the prognostic value of pretreatment ALC in oral cavity cancers with regards to both recurrence and survival. Our findings demonstrated that this hematologic marker was not significantly associated with these outcome measures in patients prior to OSCC treatment. When stratifying our sample by early and late-stage cancer, Figures 1 and 2 showed that very few early stage patients

have recurred or died. In late-stage patients, despite having a greater number of deaths and recurrences, the figures demonstrated a relatively equal distribution of normal-range ALC values for these patients in question.

The explanation behind the thought of the prognostic value of ALC is still being investigated. However, working theories include the idea that lymphocytes are important components of the adaptive immune response and thus, low ALC levels can suggest inadequate immune responses to carcinogenic processes, resulting in poorer prognoses.[15,19] In fact, immunotherapy treatments aiming to increase the efficacy of circulating lymphocytes are already being introduced into clinical practice.[20] Given the routine nature of obtaining these hematologic markers before treatment, investigations into ways to utilize these values prognostically should continue. However, given the findings of this study, efforts for oral cavity cancers in particular may be better directed toward therapies targeting other biomarkers. Studies have shown that neutrophils might contribute to tumor growth and metastasis by responding to cytokines released from tumor cells such as IL-8.[21] This finding is supported by previous reports showing the predictive value of NLR for survival in oral cavity cancers, and so, responding to the neutrophilic proliferation may be more clinically effective.

Our study was not without limitations. Given the retrospective nature of this work, we were only able to include patients in the final cohort who had complete hematologic pretreatment data and thus were only able to include 64% of all OSCC treated at our institution. Additionally, with the final sample size being small, our study should not direct future efforts away from investigating potential associations between ALC and outcomes of oral cavity cancer. Further large-scale prospective clinical studies are needed to validate these results with a more complete dataset. They should also collect and assess associations between other potential biomarkers for inflammation such as C-reactive protein, PLR or absolute neutrophil count.

5 | CONCLUSION

While the use of biomarkers, such as ALC, is promising as an affordable and accessible prognostic tool for cancer, ALC was not found to be a significant predictor for overall survival or disease-recurrence in patients with oral cavity cancer in this study. Additional investigations with greater power are needed to supplement these findings. Furthermore, research efforts analyzing other hematologic and inflammation markers are important to identify alternative vehicles for therapeutic or surveillance strategies.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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