Original Investigation | Oncology

Evaluation of Optimal Threshold of Neutrophil-Lymphocyte Ratio and Its Association With Survival Outcomes Among Patients With Head and Neck Cancer

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Abstract

IMPORTANCE Given the role of inflammation in cancer progression, neutrophil-lymphocyte ratio (NLR) from peripheral blood has been suggested as a readout of systemic inflammation and a prognostic marker in several solid malignant neoplasms. However, optimal threshold for NLR in US patients with head and neck cancer remains unclear.

OBJECTIVE To evaluate the optimal NLR threshold as a potential prognostic biomarker for survival outcomes.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study was conducted at a single institution. Participants included 496 patients with nonmetastatic head and neck cancer who underwent chemoradiation from April 2007 to March 2021. Statistical analysis was performed from September to December 2021.

EXPOSURES High vs low NLR.

MAIN OUTCOMES AND MEASURES Overall survival (OS) and cancer-specific survival (CSS).

RESULTS A total of 496 patients (411 male patients [82.9%]; 432 White patients [87.1%]; 64 patients with other race or ethnicity [12.9%]; median [IQR] age, 61 [55-67] years) were identified. Median (IQR) follow-up was 44.4 (22.8-74.0) months. Thresholds of NLR for both OS and CSS were 5.71. High NLR above 5.71 was associated with worse OS (adjusted hazard ratio [aHR], 1.97; 95% CI, 1.26-3.09; P = .003) and CSS (aHR, 2.33; 95% CI, 1.38-3.95; P = .002). On logistic multivariable analysis, patients were more likely to have high NLR if they had higher T and N staging (T3-4: aOR, 4.07; 95% CI, 1.92-9.16; P < .001; N2: aOR, 2.97; 95% CI, 1.04-9.17; P = .049; N3: aOR, 11.21; 95% CI, 2.84-46.97; P < .001), but less likely if they had a good performance status (Karnofsky Performance Status 90-100: aOR, 0.29; 95% CI, 0.14-0.59; P < .001). Among 331 patients (66.7%) with available human papillomavirus (HPV) data, high NLR was not associated with OS (HPV-negative: aHR, 2.46; 95% CI, 0.96-6.31; P = .06; HPV-positive: aHR, 1.17; 95% CI, 0.38-3.56; P = .78) and CSS (HPV-negative: aHR, 2.55; 95% CI, 0.81-7.99; P = .11; HPV-positive: aHR, 1.45; 95% CI, 0.44-4.76; P = .54).

CONCLUSIONS AND RELEVANCE High NLR was associated with worse survival. Patients with substantial disease burden and poor performance status were more likely to have high NLR. These findings suggest that further studies would be warranted to investigate the role of such prognostic marker to identify patients at risk to tailor interventions.

Key Points

Question What is an optimal threshold of neutrophil-lymphocyte ratio (NLR) as a biomarker for survival outcomes in patients with head and neck cancer who underwent chemoradiation?

Findings In this cohort study involving 496 patients, the NLR threshold was 5.71 based on maximizing log-rank test statistic. With statistical significance, high NLR above 5.71 was associated with worse overall and cancer-specific survival, and poor performance status and higher disease burden were associated with high NLR.

Meaning These findings suggest that high neutrophil-lymphocyte ratio could be an independent, adverse prognostic factor, and further studies would be warranted to tailor treatments among high-risk patients.

Introduction

Inflammation plays a major role in cancer progression.[1] Emerging biomarkers of systematic inflammation, such as elevated neutrophil-lymphocyte ratio (NLR), have been shown to be prognostic in many solid tumors.[2] Tumor cells were shown to release cytokines to stimulate the bone marrow to increase the number of neutrophils,[3-5] which in turn release cytokines promoting angiogenesis and metastasis.[6-11] Among patients with head and neck cancers, elevated NLR is an adverse prognostic marker for survival outcomes in multiple meta-analyses.[12-17]

However, studies included in such meta-analyses were heterogeneous in patient demographics and treatment characteristics suggesting the mixed strength of association between NLR and survival outcomes.[17] For example, NLR has been shown to change after induction chemotherapy and head and neck surgery,[18,19] and NLR values may differ based on racial and ethnic backgrounds.[20] In addition, the clinical utility of NLR may be challenging, because its optimal threshold remains unclear based on prior studies using its median values or predefined thresholds to stratify high vs low NLR.[17] Furthermore, the majority of these studies were performed outside the United States.[17] Given geographic heterogeneity in the prevalence of human papillomavirus (HPV)[21] and that of other risk factors including smoking and alcohol intake,[22,23] NLR values may vary based on such lifestyle factors[24] and findings from such studies may not be generalizable to patients in the United States.[20,24] To address this knowledge gap and inform clinicians to identify such potentially high-risk patients, we performed a single-institution, observational cohort study of patients treated with chemoradiation in the United States to evaluate the association of NLR and survival outcomes.

Methods

This cohort study was approved by the Roswell Park Comprehensive Cancer Center institutional review board, and informed consent was waived because the research met the criteria for minimal risk to the study participants. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Our retrospective database was built including all patients with primary head and neck cancer who underwent radiation therapy at the Roswell Park Comprehensive Cancer Center between January 2005 and April 2021. Patients were included for analysis if they were diagnosed with nonmetastatic head and neck cancer treated with curative-intent definitive chemoradiation receiving 70 Gy to gross disease and 56 Gy to elective neck lymph nodes. Intensity modulated radiation therapy (IMRT) was performed for all patients in this cohort as previously described.[25] NLR was obtained from routine complete blood counts (CBC) with differentiation, and patients with unknown NLR were excluded.

In addition to NLR prior to radiation therapy, other variables of interest included age, self-reported gender, self-reported race, smoking history, Karnofsky Performance Status (KPS), number of comorbidities, primary cancer site, cancer staging based on the American Joint Committee on Cancer (AJCC) 7th edition, HPV status, and chemotherapy agent. These variables were included for all of our multivariable analysis (MVA) models. All missing values were coded as unknown for analysis. Among patients who self-reported other racial and ethnic backgrounds, they included African American, American Indian or Alaska Native, Asian, Hispanic, and those who were unknown or declined to answer. These racial and ethnic categories were combined as a single group prior to performing our analyses, because it would be difficult to show meaningful differences in outcomes owing to small subgroup sample sizes. The primary end point of this study was overall survival (OS) and cancer-specific survival (CSS), defined as the time intervals from diagnosis to any death or last follow up and head and neck cancer-related death or last follow up, respectively.

Statistical Analysis

A threshold for NLR was determined using an outcome-based method by maximizing the log-rank test statistic and the survival differences,[26] as previously shown in other disease sites.[27-29] Such threshold was evaluated for both OS and CSS separately, and patients were then stratified into 2 cohorts by above vs below the threshold for their NLR values. Fisher exact test and Mann-Whitney U test were performed to compare baseline characteristics as appropriate. Kaplan-Meier method and log-rank tests were performed to evaluate survival outcomes. Cox MVA was used to identify variables associated with survival outcomes. Logistic MVA was performed to identify factors associated with high NLR. A subgroup analysis with Cox MVA was also performed among patients with available HPV data.

All statistical tests were 2-sided and P values lower than .05 were considered statistically significant. Statistical analyses were performed using R version 4.1.2 (R Project for Statistical Computing) from September to December 2021.

Results

Among the total of 496 patients who met the criteria for the study, 411 (82.9%) identified as male; 432 (87.1%) identified as White, 64 (12.9%) identified as other race or ethnicity; and the median (IQR) age was 61 (55-67) years (**Table 1**). The majority of patients were diagnosed with oropharyngeal cancer (n = 276; 55.6%) and underwent definitive chemoradiation with cisplatin (n = 419; 84.5%) between April 2007 and March 2021. Median (IQR) follow-up was 44.4 (22.8-74.0) months. Median (IQR) NLR was 2.8 (2.1-3.9) (**Figure 1**). Four of 496 patients (0.8%) had missing values on KPS, and 165 out of 496 patients (33.3%) had missing values on HPV status in part owing to either having nonoropharyngeal cancer or being diagnosed prior to the routine use of HPV testing (Table 1).[30] Of all patients, 71 patients (7.9%) were lost to follow up.

Thresholds of NLR for both OS and CSS were determined to be 5.71 (Figure 1). OS and CSS at 3 years were 77.3% (95% CI, 73.1%-81.7%) and 83.4% (95% CI, 79.5%-87.4%) for the low NLR cohort (P < .001); they were 43.0% (95% CI, 30.6%-60.3%) and 55.6% (95% CI, 42.9%-71.9%) for the high NLR cohort (P < .001) (**Figure 2**). On Cox MVA, high NLR was associated with worse OS (adjusted hazard ratio [aHR], 1.97; 95% CI, 1.26-3.09; P = .003) and CSS (aHR, 2.33; 95% CI, 1.38-3.95; P = .002). In addition, current smoking status, older age, poor KPS, and higher T and N staging were associated with survival outcomes (**Table 2**).

On logistic MVA, patients were more likely to have high NLR if they had higher T and N staging (T3-4: aOR, 4.07; 95% CI, 1.92-9.16, P < .001; N2: aOR, 2.97; 95% CI, 1.04-9.17; P = .049; N3: aOR, 11.21; 95% CI, 2.84-46.97; P < .001), but less likely if they had a good performance status (KPS 90-100: aOR, 0.29; 95% CI, 0.14-0.59; P < .001) (**Table 3**). A total of 331 patients (66.7%) had available HPV data. Of these, 239 patients (72.2%) had HPV-associated head and neck cancers. Median (IQR) follow-up was 43.7 (22.5-71.3) months. On Cox MVA, high NLR was not associated with OS (HPV-negative: aHR, 2.46; 95% CI, 0.96-6.31; P = .06; HPV-positive: aHR, 1.17; 95% CI, 0.38-3.56; P = .78) and CSS (HPV-negative: aHR, 2.55; 95% CI, 0.81-7.99; P = .11; HPV-positive: aHR, 1.45; 95% CI, 0.44-4.76; P = .54).

Discussion

To our knowledge, this is the largest study of US head and neck cancer patients who underwent definitive chemoradiation to evaluate the association between NLR and survival outcomes. Elevated NLR was an independent, adverse prognostic factor for both OS and CSS. Furthermore, it was associated with performance status and tumor staging.

The association of high NLR with worse survival in our study was consistent with a growing body of literature.[17] Immunosuppressive neutrophils have been implicated in tumorigenesis and tumor progression,[31-35] by remodeling tumor microenvironment, increasing tumor cell survival by

facilitating angiogenesis, and protecting tumor cells from cytotoxic activity of lymphocytes.[36,37] Specifically, tumor-associated neutrophils facilitate tumor growth by immunoediting,[38] increasing proteases to facilitate tumor invasion,[39] and activating neutrophil extracellular traps to enhance tumor adhesion and metastasis.[40] Reduction of such tumor-associated neutrophils was shown to

Table 1. Baseline Characteristics

Characteristic	Patients, No. (%)			
	All (N = 496)	Low NLR (N = 444)	High NLR (N = 52)	P value
Gender				
Male	411 (82.9)	373 (84.0)	38 (73.1)	.05
Female	85 (17.1)	71 (76.0)	14 (26.9)	
Smoker				
Never	125 (25.2)	117 (26.4)	8 (15.4)	
Current	96 (19.4)	82 (18.5)	14 (26.9)	.13
Former	275 (55.4)	245 (55.2)	30 (57.7)	
Age, y				
<65	344 (69.4)	305 (68.7)	39 (75.0)	.43
≥65	152 (30.6)	139 (31.3)	13 (25.0)	
Year of radiation				
2014 or earlier	259 (52.2)	230 (51.8)	29 (55.8)	.66
2015 or later	237 (47.8)	214 (48.2)	23 (44.2)	
KPS				
<90	135 (27.2)	107 (24.1)	28 (53.8)	
90-100	357 (72.0)	334 (75.2)	23 (44.2)	<.001
Not available	4 (0.8)	3 (0.7)	1 (1.9)	
Race				
White	432 (87.1)	387 (87.2)	45 (86.5)	.83
Other[a]	64 (12.9)	57 (12.8)	7 (13.5)	
Comorbidity				
0	77 (15.5)	68 (15.3)	9 (17.3)	
1	109 (22.0)	97 (21.8)	12 (23.1)	
2	81 (16.3)	65 (14.6)	16 (30.8)	.01
3	107 (21.6)	103 (23.2)	4 (7.7)	
>3	122 (24.6)	111 (25.0)	11 (21.2)	
Site				
Oropharynx	276 (55.6)	239 (53.8)	27 (51.9)	
Larynx	115 (23.2)	100 (22.5)	15 (28.8)	.51
Oral cavity	12 (2.4)	10 (2.3)	2 (3.8)	
Other	93 (18.8)	85 (19.1)	8 (15.4)	
T staging				
1-2	255 (51.4)	241 (54.3)	14 (26.9)	<.001
3-4	241 (48.6)	203 (45.7)	38 (73.1)	
N staging				
0	97 (19.6)	88 (19.8)	9 (17.3)	
1	52 (10.5)	46 (10.4)	6 (11.5)	
2	307 (61.9)	279 (62.8)	28 (53.8)	.10
3	40 (8.1)	31 (7.0)	9 (17.3)	
HPV				
Negative	92 (18.5)	77 (17.3)	15 (28.8)	
Positive	239 (48.2)	222 (50.0)	17 (32.7)	.04
Not available	165 (33.3)	145 (32.7)	20 (38.5)	
Chemotherapy				
Cisplatin	419 (84.5)	381 (85.8)	38 (73.1)	.02
Other	77 (15.5)	63 (14.2)	14 (26.9)	

Abbreviations: HPV, human papillomavirus; KPS, Karnofsky performance status; NLR, neutrophil-lymphocyte ratio.

[a] The other category for race and ethnicity included African American, American Indian or Alaska Native, Asian, Hispanic, and those who were unknown or declined to answer.

inhibit tumor growth, reduce immunosuppression in tumor microenvironment, and improve CD8+ cytotoxic T lymphocytes.[41-43] More recently, protumorigenic vs antitumorigenic phenotypes of tumor-associated neutrophils were found to be mediated by cytokines, such as interferon beta and transforming growth factor beta,[41,44] and the dynamic role of tumor-associated neutrophils in the context of tumor biology and microenvironment is currently evolving.[45]

Figure 1. Distribution of Neutrophil-Lymphocyte Ratio (NLR) and Threshold Evaluation Using Maximum Log-Rank Test Statistic
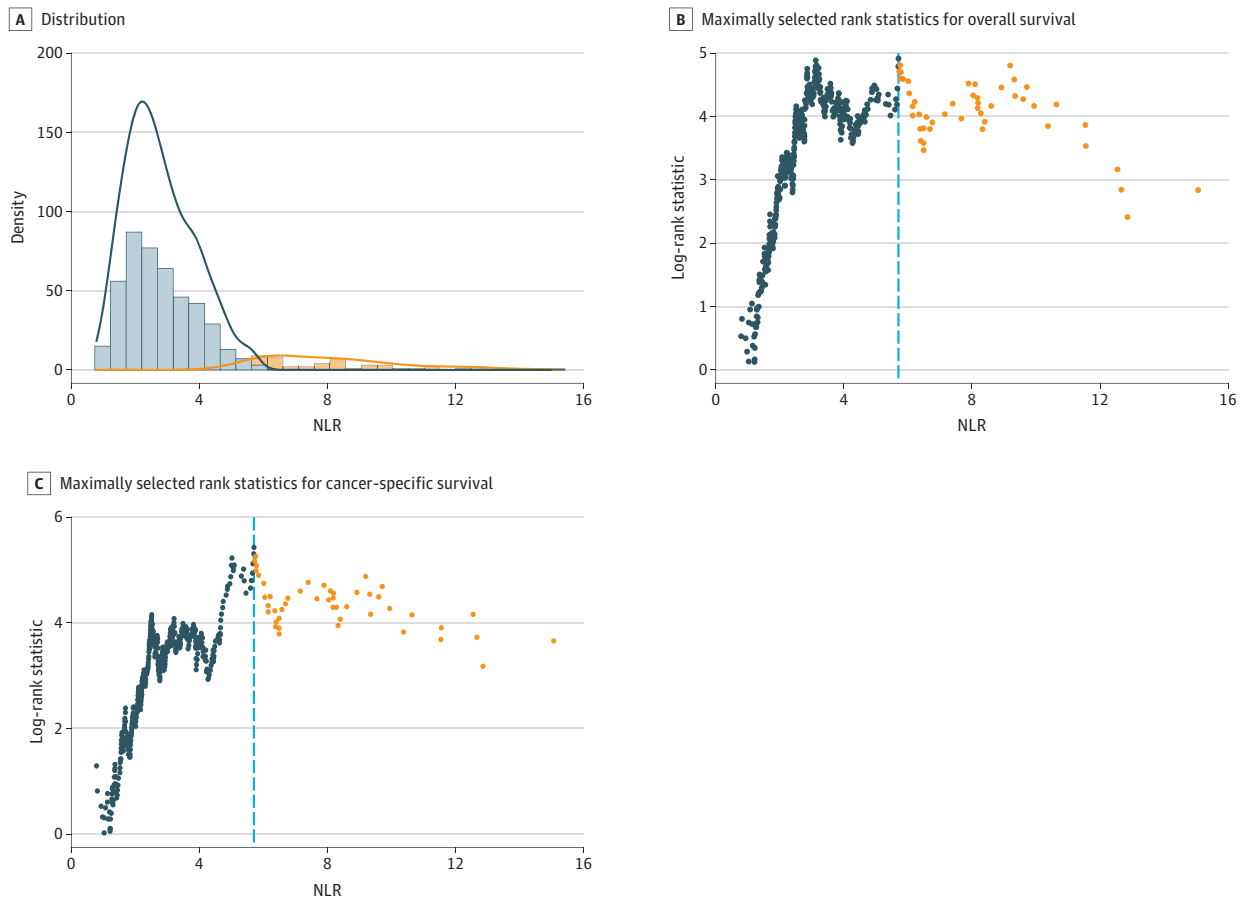

A Distribution

B Maximally selected rank statistics for overall survival

C Maximally selected rank statistics for cancer-specific survival

Figure 2. Kaplan-Meier Curve for Overall and Cancer-Specific Survival Outcomes for High vs Low Neutrophil-Lymphocyte Ratio (NLR)
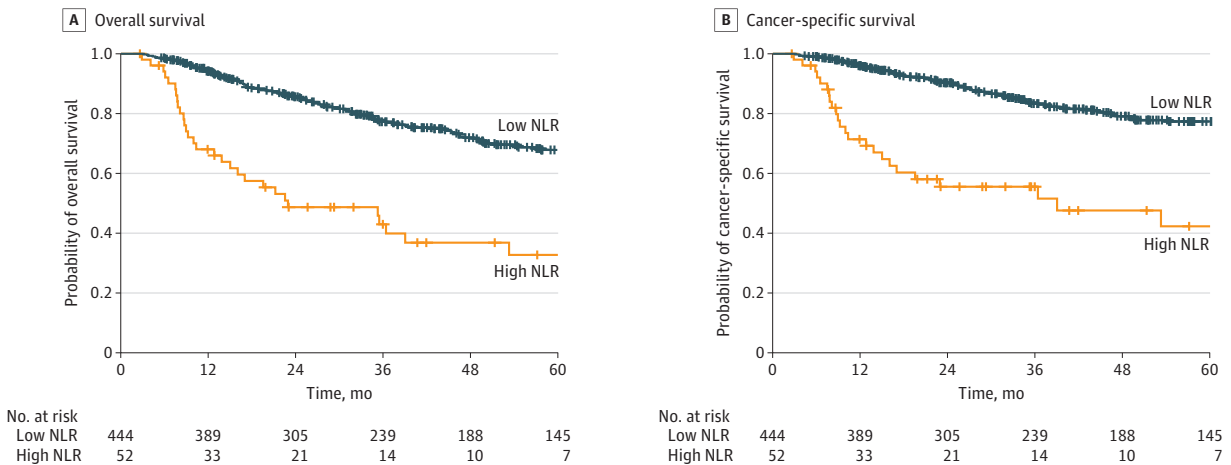

A Overall survival

No. at risk						
Low NLR	444	389	305	239	188	145
High NLR	52	33	21	14	10	7

B Cancer-specific survival

No. at risk						
Low NLR	444	389	305	239	188	145
High NLR	52	33	21	14	10	7

Table 2. Cox Multivariable Analysis for Overall and Cancer-Specific Survival

Characteristic	Overall survival		Cancer-specific survival	
	aHR (95% CI)	P value	aHR (95% CI)	P value
NLR				
Low	1 [Reference]	NA	1 [Reference]	NA
High	1.97 (1.26-3.09)	.003	2.33 (1.38-3.95)	.002
Gender				
Male	1 [Reference]	NA	1 [Reference]	NA
Female	0.86 (0.56-1.32)	.49	0.72 (0.41-1.26)	.25
Smoker				
Never	1 [Reference]	NA	1 [Reference]	NA
Current	2.02 (1.22-3.35)	.006	1.73 (0.90-3.30)	.1
Former	1.2 (0.78-1.85)	.41	1.22 (0.69-2.14)	.5
Age, y				
<65	1 [Reference]	NA	1 [Reference]	NA
≥65	1.89 (1.33-2.69)	<.001	1.73 (1.09-2.74)	.02
Year of radiation				
2014 or earlier	1 [Reference]	NA	1 [Reference]	NA
2015 or later	0.91 (0.63-1.32)	.62	1.09 (0.70-1.70)	.7
KPS				
<90	1 [Reference]	NA	1 [Reference]	NA
90-100	0.77 (0.53-1.11)	.16	0.46 (0.29-0.73)	<.001
Race				
White	1 [Reference]	NA	1 [Reference]	NA
Other[a]	1.41 (0.91-2.16)	.12	1.6 (0.93-2.74)	.09
Comorbidity				
0	1 [Reference]	NA	1 [Reference]	NA
1	0.63 (0.37-1.09)	.1	0.6 (0.31-1.16)	.13
2	1.02 (0.57-1.79)	.96	0.6 (0.29-1.25)	.17
3	0.43 (0.23-0.81)	.008	0.37 (0.17-0.79)	.01
>3	1.21 (0.70-2.09)	.49	0.91 (0.47-1.78)	.78
Site				
Oropharynx	1 [Reference]	NA	1 [Reference]	NA
Larynx	1.16 (0.72-1.86)	.55	1.32 (0.72-2.40)	.37
Oral cavity	1.32 (0.60-2.94)	.49	2.17 (0.84-5.62)	.11
Other	1.03 (0.66-1.62)	.9	1.39 (0.77-2.49)	.27
T staging				
1-2	1 [Reference]	NA	1 [Reference]	NA
3-4	2.40 (1.70-3.40)	<.001	3.85 (2.41-6.14)	<.001
N staging				
0	1 [Reference]	NA	1 [Reference]	NA
1	1.89 (1.02-3.50)	.04	2.35 (1.05-5.28)	.04
2	2.06 (1.26-3.36)	.004	3.46 (1.79-6.68)	<.001
3	5.43 (2.81-10.51)	<.001	8.41 (3.47-20.36)	<.001
HPV				
Negative	1 [Reference]	NA	1 [Reference]	NA
Positive	0.67 (0.41-1.11)	.12	0.71 (0.38-1.34)	.29
Chemotherapy				
Cisplatin	1 [Reference]	NA	1 [Reference]	NA
Other	1.45 (0.94-2.25)	.09	1.41 (0.79-2.50)	.24

Abbreviations: aHR, adjusted hazard ratio; HPV, human papillomavirus; KPS, Karnofsky performance status; NA, not applicable; NLR, neutrophil-lymphocyte ratio.

[a] The other category for race and ethnicity included African American, American Indian or Alaska Native, Asian, Hispanic, and those who were unknown or declined to answer.

Consistent with prior studies,[46,47] we found that patients with higher disease burden were more likely to have elevated NLR. Similarly, elevated NLR was associated with worse performance status and the use of chemotherapy agents other than cisplatin in our study. Patients who are unsuitable to tolerate toxicity and morbidity from platinum-based chemotherapy may undergo other systemic therapy agents,[48] and this association with poor performance status is consistent with elevated NLR associated with malnutrition, weight loss, and cancer cachexia.[49] Elevated NLR remained independently associated with OS and CSS even after adjusting for these and other factors.

Table 3. Logistic Multivariable Analysis for High Neutrophil-Lymphocyte Ratio

Characteristic	aOR (95% CI)	P value
Gender		
Male	1 [Reference]	NA
Female	2.18 (0.95-4.91)	.06
Smoker		
Never	1 [Reference]	NA
Current	1.50 (0.50-4.64)	.47
Former	1.18 (0.46-3.26)	.73
Age, y		
<65	1 [Reference]	NA
≥65	0.46 (0.20-1.03)	.07
Year of radiation		
2014 or earlier	1 [Reference]	NA
2015 or later	0.98 (0.48-1.99)	.96
KPS		
<90	1 [Reference]	NA
90-100	0.29 (0.14-0.59)	<.001
Race		
White	1 [Reference]	NA
Other[a]	0.63 (0.20-1.68)	.38
Comorbidity		
0	1 [Reference]	NA
1	0.66 (0.23-1.97)	.45
2	1.38 (0.47-4.15)	.56
3	0.18 (0.04-0.70)	.02
>3	0.37 (0.11-1.19)	.10
Site		
Oropharynx	1 [Reference]	NA
Larynx	1.30 (0.46-3.61)	.62
Oral cavity	1.88 (0.20-11.95)	.54
Other	0.81 (0.27-2.19)	.68
T staging		
1-2	1 [Reference]	NA
3-4	4.07 (1.92-9.16)	<.001
N staging		
0	1 [Reference]	NA
1	2.16 (0.55-8.10)	.26
2	2.97 (1.04-9.17)	.049
3	11.21 (2.84-46.97)	<.001
HPV		
Negative	1 [Reference]	NA
Positive	0.45 (0.16-1.19)	.11
Chemotherapy		
Cisplatin	1 [Reference]	NA
Other	4.24 (1.74-10.36)	.001

Abbreviations: aOR, adjusted odds ratio; HPV, human papillomavirus; KPS, Karnofsky performance status; NA, not applicable.

a The other category for race and ethnicity included African American, American Indian or Alaska Native, Asian, Hispanic, and those who were unknown or declined to answer.

Among patients with available HPV data, our study found that high NLR was not associated with survival. This finding is consistent with a prior report.[50] In contrast, other studies found that high NLR was an adverse prognostic factor for survival outcomes even in the HPV era.[18,51-54] In addition, another study suggested HPV-associated head and neck cancers were also less likely to have high NLR,[53] which was not observed in our study. These discrepancies may be due to the heterogeneous nature of tumor biology among HPV-associated head and neck cancers based on smoking history.[30] Nearly 80% of patients in our study were either former or current smokers, and smoking has been shown to alter tumor gene expressions and tumor microenvironment, leading to changes in inflammation and immune-related pathways.[55,56]

Limitations

This study has limitations, including those inherent in retrospective reviews. The neutrophils from our study were not isolated for further characterization of their phenotypes, and the heterogeneity of protumorigenic and antitumorigenic neutrophil phenotypes could not be evaluated in our study. Although several studies showed a prognostic role of dynamic changes in NLR in various cancers,[57-60] our data on NLR after radiation therapy were missing in many patients and were not included for analysis in this study. In addition, the association between low NLR and survival would warrant further investigations, because febrile neutropenia may occur up to 15% with concurrent cisplatin.[61] Toxicity profiles including infection and febrile neutropenia were unavailable for analysis in our study. Furthermore, most patients in our study were White individuals treated with chemoradiation. Our findings may not be generalizable to other populations with different treatment modalities and racial backgrounds.[18-20,24]

Conclusions

Our study's findings suggested that high NLR was an independent adverse prognostic factor for survival outcomes among patients with head and neck cancer undergoing chemoradiation. Patients with substantial disease burden and poor performance status were more likely to have high NLR. Further studies would be warranted to tailor treatments based on the risk stratification by NLR.

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