

# Prognostic Value of Preoperative Neutrophil-to-Lymphocyte Ratio in Adenoid Cystic Carcinoma of the Head and Neck

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## Research

**Keywords:** Adenoid cystic carcinoma, Neutrophil-to-lymphocyte ratio, Prognosis, Survival

**Posted Date:** November 15th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-1048936/v1>

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# Abstract

## Background

Studies in recent years have shown that the neutrophil-to-lymphocyte ratio (NLR) is associated with the survival and prognosis of patients with malignant tumors. However, the utility of the NLR in predicting outcomes in patients with adenoid cystic carcinoma (ACC) of the head and neck remains unclear. Here, we examined the prognostic value of the preoperative NLR in patients with ACC of the head and neck.

## Methods

This study retrospectively analyzed 71 patients with a histopathological diagnosis of ACC from August 2005 to November 2020. The optimal cutoff value was obtained by receiver operating characteristic (ROC) analysis. The characteristics of the patients were evaluated using chi-squared tests. The value of the NLR used in predicting the outcomes of these patients was analyzed using Kaplan-Meier curves and Cox regression models.

## Results

The cutoff value of the NLR was 2.071. The chi-squared tests showed that a high NLR (>2.071) was associated with tumor stage and lymph node metastasis (LNM). Kaplan-Meier survival analysis showed that the NLR > 2.071 group was correlated with a shorter Overall survival ( $P < 0.05$ ). In multivariate Cox regression analysis, high NLR (>2.071) and high age (>54 years) were independent risk factors predicting poorer outcomes in patients with ACC.

## Conclusions

We suggest that the preoperative NLR is a useful biomarker for the prognosis of patients with ACC.

## Background

Adenoid cystic carcinoma (ACC) is a rare malignant tumor with an annual incidence of 3–4.5 cases per million people<sup>1</sup>, accounting for approximately 1% of all head and neck malignancies and 10% of all salivary gland tumors and is the most commonly reported malignancy of the minor salivary glands<sup>2</sup>. Unfortunately, ACC is still a poorly understood disease due to its unpredictability, the need for long-term follow-up and the paucity of available clinical trials<sup>3</sup>. Therefore, it is of great significance to correctly evaluate the prognosis of patients with ACC. Traditional prognostic indicators, including the presence of metastasis, tumor grade, histological subtype, and tumor volume, have gradually shown inaccuracy and inadequacy in clinical practice<sup>4</sup>. Identification of highly available and noninvasive prognostic factors could help us identify high-risk patients and provide them with the best therapy protocol, which may lead to further improvement of treatment outcomes<sup>5</sup>.

Many studies have illustrated a strong connection between cancer and inflammation<sup>6</sup>. Inflammatory cells are significant tumor promoters early in the neoplastic process. Cancer-related inflammation enables cancer cells to form malignant biological behaviors, including proliferation, infiltration, angiogenesis, and metastasis<sup>7</sup>. In the past few years, many studies have shown that there are multiple inflammatory responses associated with poor outcomes in many types of malignancies, such as adrenocortical carcinoma, gastric cancer and ampullary carcinoma<sup>8-10</sup>. Inflammatory and hematological markers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR), have been used to guide treatment and predict prognosis in cancer patients.

The absolute value of neutrophils reflects the body's inflammatory response caused by tumors, while the absolute value of lymphocytes reflects the body's antitumor immune suppression level. The detection of the NLR as a systemic immune-inflammation index is useful to predict the prognosis of head and neck squamous cell carcinoma<sup>11</sup>, and thus far, only two studies have examined the NLR in ACC<sup>12,13</sup>. In these studies, only 17 and 29 patients had available NLR data, respectively, so the conclusions of these studies were not quite convincing. Therefore, our study was designed to evaluate the NLR as a prognostic marker in a relatively larger group of patients with ACC.

## Methods

### Study population

This retrospective study included 71 patients diagnosed with ACC at Xuzhou Central Hospital (Xuzhou, China) from August 2005 to November 2020. The criteria for enrollment in this study were as follows: (1) at least 18 years of age; (2) primary tumor sites located in the head and neck region; (3) pathological diagnosis clearly defined as ACC; (4) treatment modalities including surgery as well as combined surgery and postoperative radiotherapy; (5) no other tumors detected; and (6) complete preoperative routine blood and biochemical examinations. Patients with any detectable inflammatory disease were excluded.

### Laboratory and clinical data

Baseline characteristics of the patients included age, sex, disease stage, tumor

site, treatment, perineural invasion, and LNM. For the aim of the

analysis, the tumor-node-metastasis (TNM) stage of disease was divided as follows: stages I and II were regarded as early stage, whereas stages III and IV were regarded as advanced stage. This was done according to classification following the criteria of the TNM Classification of Malignant Tumors, Eighth Edition<sup>14</sup>. Designatesurgeonswith extensive experience in standardized treatment, emphasizing radical excision of the primary lesion. Intraoperative frozen section examination was used as much as possible to ensure safe surgical margins, tracing of the involved nerve, and removal of surrounding tissues that are likely to be invaded by the tumor. If preoperative examination revealed suspicious lymph nodes and positive frozen sections, cervical lymph node dissection was performed at the same time. Radiotherapy

was usually performed within 4-6 weeks postoperatively. If patients had poor wound healing, radiotherapy was delayed appropriately (no more than 8 weeks). All patients were scanned with a 3 mm layer thickness, and the extent of the scan was determined by the location of the lesion, including at least 3 cm above the skull base to 3 cm below the clavicle. Clinical tumor volume (CTV) was outlined to include the preoperative primary tumor area and postoperative tumor bed area, as well as the neck subdivision where the metastatic lymph nodes were located. For those with definite cranial nerve invasion, the CTV also involved the extent of cranial nerve travel to block the potential recurrence pathway. The planned target volume (PTV) is a three-dimensional extrapolation of 3 mm from the CTV; 66 Gy was prescribed for patients with positive margins and 54-60 Gy for the remaining patients, with fractional doses of 1.8 to 2.0 Gy/dose. Blood samples were obtained prior to the initiation of treatment. Neutrophil count, lymphocyte count and platelet count were used as serological indicators of inflammation. The NLR was calculated by dividing the absolute neutrophil count (count/ $\mu\text{L}$ ) by the absolute lymphocyte count (count/ $\mu\text{L}$ ), while the PLR was calculated by dividing the absolute platelet count (count/ $\mu\text{L}$ ) by the absolute lymphocyte count (count/ $\mu\text{L}$ ). Overall survival (OS) was defined as the time from diagnosis to death, and disease-free survival (DFS) was defined as the time from treatment start to the recurrence of the disease or death from any cause.

## Statistical analysis

Time-dependent ROC curves were made by R program. The optimal cutoff value was determined by ROC analysis. The characteristics of the patients were analyzed using chi-squared tests. The survival curves were plotted using the Kaplan-Meier method, and the significance was determined through the log-rank test. Univariate and multivariate analyses were performed by the Cox proportional hazard model. Statistical analyses were performed using a statistical analysis software package (SPSS Statistics, version 25; IBM, Armonk, NY, USA), and  $P$  values  $<0.05$  were considered significant.

## Results

### Detection of the cutoff value of the NLR

The ideal cutoff value for the preoperative NLR was 2.071, according to the time-dependent ROC curve. The ROC area under the curve (AUC) for the NLR was 0.743 (3 years). The AUC was 0.5-0.7, indicating poor predictive value, while 0.7-0.9 showed moderate predictive value<sup>15</sup>. The ROC curve of the PLR did not manifest a significant value of predictability.

### Correlation of NLR with the clinical and pathologic characteristics of patients with ACC

We examined a total of 71 patients, including 28 (39.44%) males and 43 (60.56%) females. The median OS and DFS in the study population were 54.0 months (95% CI 40.0-68.0) and 43.0 months (95% CI 31.0-55.0), respectively.

As shown in Table 1, the median age was  $54 \pm 25$  years. The tumors of these patients were located in a major salivary gland (29.58%), minor salivary gland (50.70%) and other sites (19.72%), respectively. Surgery alone was performed on 28 (39.44%) patients. Surgery and adjuvant radiation were used on 43 (60.56%) patients.

As presented in Table 1, the correlation between the preoperative NLR and clinical and pathologic characteristics was evaluated. Thirty-seven (52.11%) patients (NLR > 2.071) were included in the high NLR group, and 34 (47.89%) patients were distributed to the low NLR (NLR  $\leq$  2.071) group.

The preoperative NLR level was closely related to the TNM stage and LNM ( $P < 0.05$ ). No obvious correlations with age, sex, location, treatment or perineural invasion were observed ( $P > 0.05$ ).

Table 1 ACC patients (n=71) categorized by NLR and their clinical pathologic characteristics.

Clinical character		NLR		P-value
		$\leq 2.071$ (n=34)	$> 2.071$ (n=37)	
Age	$\leq 54$	18	19	0.893
	$> 54$	16	18	
Gender	Male	15	13	0.439
	Female	19	24	
Location	Major Salivary Gland	10	11	0.555
	Minor Salivary Gland	19	17	
	Other	5	9	
TNM Stage	I / II	9	35	0.000
	III / IV	25	2	
Treatment	Surg Alone	13	15	0.843
	Surg & adjuvant Rad	21	22	
Perineural invasion	No	7	8	0.98
	Yes	25	29	
LNM	No	30	25	0.037
	Yes	4	12	

NLR neutrophil-to-lymphocyteratio, TNM tumor-node-metastasis, LNM lymph-node-metastasis

## The relationship of the NLR with postoperative OS and DFS in patients with ACC

Kaplan-Meier survival analysis showed that the NLR > 2.071 group was correlated with

a shorter OS ( $P < 0.05$ ), while the NLR had no relationship with DFS (Fig. 2).

As seen in the univariate analysis in Table 2, we found that age (HR 3.67, 95% CI

[1.34-10.08]) and NLR (HR 4.85, 95% CI [1.60–14.67]) were associated with OS in patients with ACC ( $P < 0.05$ ) but had no relationship with DFS. Sex, TNM stage, LNM and perineural invasion were not significantly related to either OS or DFS ( $P > 0.05$ ).

In the multivariate analysis, we found that the NLR (HR 0.22, 95% CI [0.07–0.66]) and age

(HR 0.31, 95% CI [0.12-0.81]) were independent risk factors for OS in patients with

ACC.

Table 2 Univariate and multivariate analyses of prognostic factors with OS and DFS in patients with ACC (n=71)

Clinicopathologic variable	OS		DFS	
	HR(95%CI)	P-value	HR(95%CI)	P-value
<b>Univariate analysis</b>				
Gender (male vs. female)	0.64(0.24-1.70)	0.37	0.92(0.39-2.16)	0.85
Age, years (>54 vs. ≤54)	3.67(1.34-10.08)	0.012	0.46(0.17-1.27)	0.13
TNM (III/IV vs. I/II)	1.78(0.72-4.39)	0.215	1.38(0.59-3.23)	0.46
LNM (presence vs. absence)	1.49(0.49-4.56)	0.15	1.81(0.66-4.96)	0.25
Perineural invasion (presence vs. absence)	1.40(0.41-4.82)	0.59	1.12(0.38-3.33)	0.84
NLR (>2.071 vs. ≤2.071)	4.85(1.60-14.67)	0.005	0.81(0.34-1.94)	0.631
<b>Multivariate analysis</b>				
Age, years (>54 vs. ≤54)	0.31(0.12-0.81)	0.017		
NLR (>2.071 vs. ≤2.071)	0.22(0.07-0.66)	0.007		

NLR neutrophil-to-lymphocyteratio, TNM tumor-node-metastasis, LNM lymph-node-metastasis

## Discussion

In this analysis of 71 patients with ACC, we found that the preoperative NLR can be a predictive biomarker for OS in ACC and is related to TNM stage and the LNM. Participants were divided into two groups according to the cutoff value, and chi-squared tests were applied to evaluate the clinical and pathologic characteristics of patients with ACC. We found that the preoperative NLR I was closely related to the TNM stage and LNM ( $P < 0.05$ ). No obvious correlations with age, sex, location, treatment or perineural invasion were observed ( $P > 0.05$ ). We used Kaplan-Meier survival analysis to determine the relationship between the NLR and OS and the NLR and DFS. Patients with a NLR >2.071 had a shorter OS ( $P < 0.05$ ), and the

NLR was not associated with DFS ( $P > 0.05$ ). We used a Cox regression model and analyzed sex, age, TNM stage, nerve invasion, LNM and NLR of patients. We found that the NLR (HR 0.22, 95% CI [0.07–0.66]) and age (HR 0.31, 95% CI [0.12–0.81]) were independent risk factors for OS in patients with ACC. The finding that a high NLR ( $> 2.071$ ) was a strong indicator of OS in patients with ACC appears to be novel.

Neutrophils display a protumor phenotype that could be detrimental to the host. The tumor microenvironment controls neutrophil recruitment, and in turn, neutrophils can strengthen the biological behavior of the tumor, causing it to grow and metastasize<sup>16</sup>. The mechanisms for this phenotype are just beginning to be demonstrated, but some of them involve genotoxicity, angiogenesis, and immunosuppression. It can change the tumor microenvironment by producing cytokines and chemokines and can also promote the transformation of normal cells into tumor cells by secreting reactive oxygen species and proteases and promoting cell migration and diffusion<sup>17</sup>. Liu reported that tumor-infiltrating neutrophils were related to the OS of patients with non muscle invasive bladder cancer (NMIBC)<sup>18</sup>.

Lymphocytes are the strongest parts of the adaptive immune system, which upon invasion of the tumor manifest the formation of an effective antitumor cellular immune response<sup>19</sup>. Elevated CD4+ and CD20+ lymphocytes in tumors have a strong relationship with improved disease-specific survival in patients who have undergone wide resections<sup>20</sup>. Lymphocytic cytokines secreted by the tumor could lead to a decrease in lymphocyte counts in a cancer patient, where lymphocytes undergo activation-induced apoptosis<sup>21</sup>. Seoung Yoon Rho reported that the circulating total lymphocyte count alone could be associated with immunologic parameters in patients with left-sided pancreatic cancer. In addition, it may affect the oncological outcome, regardless of tumor biology<sup>22</sup>.

Higher neutrophil levels can upregulate the expression of growth factors, such as chemokines, which play an important role in tumor development and progression. The reduction in lymphocytes indicates that the body's immunity is reduced and its antitumor ability is weakened. An increased NLR indicates that the body's inflammatory response is increased, while the lymphocyte-mediated antitumor response is decreased, which can easily cause tumor deterioration and metastasis, ultimately leading to the poor prognosis of patients<sup>15,16,17,23,24</sup>. Takumi Hasegawa et al. reported that the NLR increased with the number of pathological lymph node metastases and shorter OS in patients with oral cancer, which was also an indication of a decrease in the lymphocyte count<sup>25</sup>. The results of a meta-analysis suggested that an elevated pretreatment NLR is a negative prognostic factor in patients with head and neck cancer<sup>26</sup>.

One of the results of our study showed that the NLR had a relationship with the TNM stage, which confirmed the findings of Sibel Goksel, who was able to demonstrate that a higher NLR could be a robust predictor to distinguish advanced stages of lung cancers<sup>27</sup>. A high NLR implies relative lymphocytopenia and neutrophilic leukocytosis. The former indicates a decrease in lymphocyte-mediated anticancer effects<sup>17</sup>, and the latter indicates higher secretion of proangiogenic factors for tumor growth<sup>23</sup>, which may partly explain the connection between the NLR and TNM stage.

One point worth mentioning is that an association between the LMN and NLR has been found in our research, which is the first one that was illustrated in ACC. This relationship has already been demonstrated in many other cancers, such as esophageal squamous cell carcinoma, endometrial cancer and resectable pancreatic neuroendocrine tumors<sup>28-30</sup>. This conclusion still needs to be further confirmed through more studies concerning the ACC to improve its validity.

Perineural invasion had no significant association with the preoperative NLR, which had been proved in published data<sup>31</sup>.

Chun-Ye Zhang et al. analyzed 218 cases of ACC of the head and neck (ACCHN) and reported that older age (>60 years) is a significant factor for predicting poor prognosis in Chinese patients with ACCHN<sup>32</sup>. Yunsuk Choi et al. also reported that older people with ACCHN tend to have shorter OS<sup>33</sup>. Our multivariate analysis indicated that older age (>54 years) is an independent predictor for the low survival of patients with ACC, which is largely in concordance with the results mentioned above. Comorbidities and worse performance status may lead to a poorer prognosis for elderly patients.

Kizuki Yuza et al. found that the TNM stage clearly predicted outcomes of postoperative patients with gallbladder carcinoma. This is not in accordance with our results, which showed that patients with advanced TNM stage were prone to shorter OS, but it had no statistical significance<sup>34</sup>. Several studies have demonstrated a positive correlation between LNM and decreased survival in patients with ACC of the head and neck<sup>35-37</sup>. Although our univariate analysis showed that patients with LNM were prone to shorter OS, it had no statistical significance (Table 2). Therefore, more cases need to be enrolled to prove our findings of patients with ACC.

Our present study has several limitations. First, because the optimal cutoff values for the NLR vary according to the clinical and pathological characteristics of participants and the number of participants, the cutoff value we obtained from the ROC curve is not generalizable to all patients with ACC. Second, because of the single-center design and rarity of ACC, our findings involved a sample that was relatively small. Although multivariate analysis was performed to reduce the bias, caution should still be used when dealing with the results of our research. Therefore, further multicenter prospective studies are needed to validate the sensitivity and specificity of the NLR in evaluating the prognosis of ACC.

In conclusion, a high NLR was associated with advanced tumor stage and LNM, as well as correlated with a shorter OS. In multivariate Cox regression analysis, a high NLR and older age were independent risk factors predicting poorer outcomes in patients with ACC. Therefore, we hypothesized that the preoperative NLR was a useful biomarker for the prognosis of patients with ACC.

## Abbreviations

### NLR

Neutrophil-to-lymphocyte ratio

**ACC**

Adenoid cystic carcinoma

**ROC**

Receiver operating characteristic

**LNМ**

Lymph node metastasis

**PLR**

Platelet-to-lymphocyte ratio

**LMR**

Lymphocyte-to-monocyte ratio

**TNM**

Tumor-node-metastasis

**CTV**

Clinical tumor volume

**PTV**

Planned target volume

**OS**

Overall survival

**DFS**

Disease-free survival

**AUC**

Area under the curve

**NMIBC**

Nonmuscle invasive bladder cancer

**ACCHN**

Adenoid cystic carcinoma of the head and neck

## Declarations

### Ethical approval

Ethical approval was obtained from the Ethics Committee of Xuzhou Central

Hospital(XZXY-LK-20211007-032).

### Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/parent/guardian/ relative of the patient. A copy of the consent form is available for review by the Editor of this journal.

### Availability of data and materials

**The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.**

## **Competing interests**

We wish to confirm that there are no known conflicts of interest associated with this publication.

## **Funding**

This study was supported by grants from the National Clinical Research Center for Oral Diseases (NCRCO-202101).

## **Authors' contributions**

XRL and JM conceived and designed the experiments. XRL, LZ, YXC and NL performed the experiments. XRL and LZ analyzed the data. XRL and JM wrote the manuscript. All authors read and approved the final manuscript.

## **Acknowledgements**

The authors would like to thank all of the authors who contributed to this paper and all of the patients in our study.

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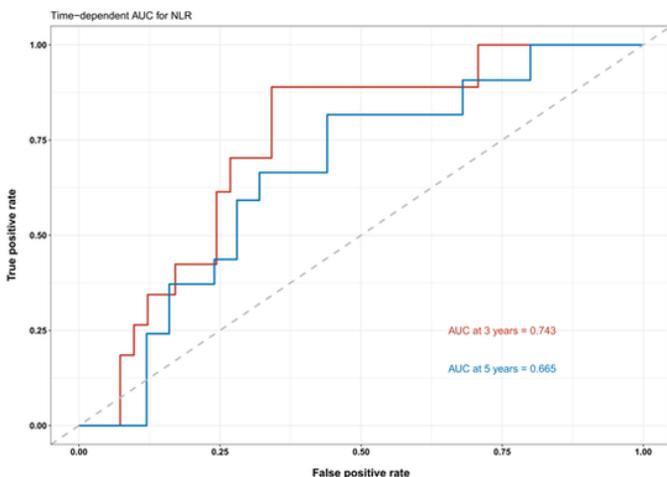
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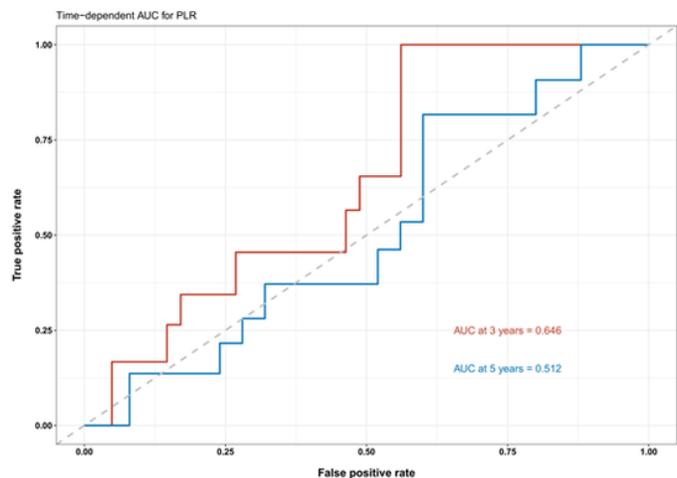
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## Figures

A

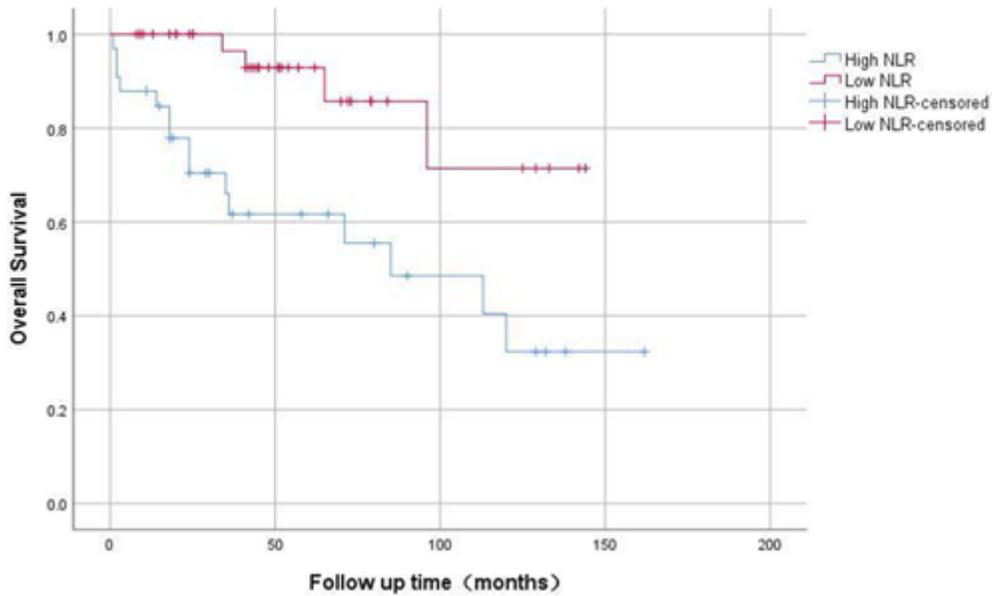


B



**Figure 1**

The ROC curves of the NLR and PLR in patients with ACC. (A) The ROC area of NLR was 0.743(3 years). (B) The ROC area of PLR was 0.646(3 years).



**Figure 2**

Kaplan–Meier survival analysis indicates that patients with a NLR >2.071 have a shorter OS.