


# Prognostic Value Of The Preoperative Neutrophil To Lymphocyte Ratio In Patients With Sinonasal Squamous Cell Carcinoma

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**Objective:** This study explored the effectiveness of a new inflammatory prognostic system, using preoperative neutrophil to lymphocyte ratio (NLR) to predict the postoperative survival rate of patients with sinonasal squamous cell carcinoma (SSCC).

**Methods:** Patients diagnosed with SSCC who undergone surgically treated without neoadjuvant therapy were included in the study between May 2008 and October 2017. Preoperative NLR is defined as: preoperative neutrophil/postoperative lymphocyte ratio. The prognostic value was uncovered by univariate and multivariate Cox hazards analysis.

**Results:** A total of 147 patients were included in this study. Through the multivariate analysis, pathological T stage (hazard ratio [HR] 1.719, confidence interval [CI] 1.277–3.642,  $p < 0.001$ ), pathological N stage (HR 1.344, 95% CI 1.015–2.776,  $p < 0.001$ ), and preoperative NLR (HR 1.579, 95% CI 1.217–3.092,  $p = 0.002$ ) were independent risk factor for overall survival (OS). Pathological T stage (HR 1.835, 95% CI 1.141–3.132,  $p < 0.001$ ), pathological N stage (HR 1.281, 95% CI 1.169–2.476,  $p < 0.001$ ), and preoperative NLR (HR 1.688, 95% CI 1.162–3.363,  $p < 0.001$ ) were also independently associated with disease-free survival (DFS). Pathological T stage (HR  $p < 0.001$ , 95% CI 1.537–3.021,  $p < 0.001$ ), pathological N stage (HR 1.571, 95% CI 1.157–2.258,  $p < 0.001$ ), and preoperative NLR (HR 1.509, 95% CI 1.153–3.104,  $p = 0.001$ ) were independent risk factors for disease-specific survival (DSS).

**Conclusion:** The preoperative NLR is considered to be a useful predictor of postoperative survival in SSCC patients.

**Keywords:** sinonasal carcinoma, albumin-to-globulin ratio, patients, risk factor, survival

## Introduction

Among head and neck tumors, the incidence and mortality of SSCC are relatively high, among which the most common type is squamous cell carcinoma.<sup>1,2</sup> Difficult anatomic localization and early lymph node metastasis determine poor prognosis of SSCC. Endoscopic resection and lateral rhinotomy are still the main surgical methods, but complex anatomy and bone obstruction make complete resection of SSCC difficult.<sup>3,4</sup> Stratified management of SSCC patients is of great significance for selecting treatment mode. Therefore, using a simple, convenient and inexpensive index to predict the prognosis of SSCC patients is of great significance for the determination of clinical treatment regimens.

In recent years, more and more evidence show that blood index has a definite significance in predicting the prognosis of tumor patients. Elevated levels of neutrophils are considered a marker of local and systemic inflammation, and their

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production of cytokines and angiogenic factors significantly promotes tumor development.<sup>5,6</sup> As an important defense of the immune system, lymphocytes are related to the body's immune surveillance.<sup>7,8</sup> Preoperative NLR represents the preoperative neutrophil/postoperative lymphocyte ratio, maybe more helpful for patients with tumor prognosis prediction. Previous studies have shown that preoperative elevation of NLR is an independent predictor of poor prognosis in non-metastatic papillary renal cell carcinoma.<sup>9</sup> In a 16-year follow-up study of 527,124 Korean adults, the NLR was independently associated with an increased risk of lung cancer mortality.<sup>10</sup> However, the predictive role of NLR in SSCC has been unclear due to the lack of literature. Since NLR is an important prognostic factor for multiple tumors, we hypothesized the indicator is also associated with the prognosis of SSCC. The purpose of this study was to evaluate the predictability of preoperative NLR to long-term mortality after the operation of SSCC patients.

## Materials And Methods

### Patients

The study was approved by the ethics committee of the West China Hospital of Sichuan University and has been performed in accordance with the ethical standards laid down in an appropriate version of the Declaration of Helsinki (as revised in Brazil 2013). Patients who only underwent tumor resection at the hospital between May 2008 and October 2017 took part in this study. Postoperative pathological diagnosis was SSCC. The exclusion criteria are as follows: connective tissue disease or other diseases that affect blood cell lines; patients who stopped treatment during hospitalization; patients with liver impairment; and patients receiving preoperative anti-tumor therapy (including antitumor therapy). All patients underwent blood cell tests, coagulation, nasal endoscopy, abdominal ultrasonography, head and neck computed tomography or magnetic resonance imaging and chest radiography 3 days before was given a form of treatment. If multiple tests are performed, the results of the first test will be the standard. Preoperative NLR is meant by preoperative neutrophil/preoperative lymphocyte.

### Follow-Up

First follow-up was conducted in the first month after surgically treated SSCC and every three months. Postoperative items include blood cell detection, coagulation, electron fiber

laryngoscope, abdominal ultrasound, head and neck magnetic resonance imaging (MRI) or computed tomography (CT), and chest CT. A positive nasal endoscopic biopsy suggested recurrence.

## Statistical Methods

For statistical analysis, statistical Package for social sciences 21(SPSS21) (SPSS Inc., Chicago, IL, USA) was utilized. This is a retrospective chart review. The cut-off point for preoperative NLR was determined by the median value. Variables with a  $p$  value  $< 0.05$  in the univariate analyses were selected for multivariate analyses by Cox regression. The survival curve was estimated by Kaplan-Meier analysis, and the log rank test was used to examine the significance of differences in survival distribution between groups.  $P < 0.05$  was considered statistically significant.

## Results

### Patient Characteristics

Of the 147 patients enrolled, 123 were men, and 24 were women. The age was  $61.33 \pm 13.31$  years. As showed in [Table 1](#), there were 21 non-smokers and 126 smokers and with an average body mass index (BMI) of  $24.13 \pm 3.31$  kg/m<sup>2</sup>. The number of patients with tumor size  $< 2.5$ cm and  $\geq 2.5$ cm was 89 and 58, respectively. Three pathological types (G1, G2 and, G3) numbers were 31, 84 and 32, respectively. Four pathological types (T1, T2, T3 and T4) numbers were 21, 61, 33 and 32, respectively. There were 51 patients with negative pathological N stage (NX, N0) and 96 patients with positive pathological N stage (N1, N2, N3). In all, 44 patients received endoscopic surgery, while 103 received nasal endoscopic combined with lateral rhinotomy ([Table 1](#)). The duration of follow up for the survivors was  $39.21 \pm 15.36$  months with a mean duration of overall survival of  $38.44 \pm 14.69$  months, disease free survival of  $38.13 \pm 14.04$  months and disease specific survival of  $37.47 \pm 13.15$  months. 32 patients received radiotherapy and 14 patients received chemotherapy. 68 patients suffered recurrence (46.3%) and 83 patients died during follow-up (56.5%). The 5-year OS, DSS, and DFS rates for all patients were 59.4%, 61.3%, and 52.8%, respectively ([Figure 1](#)).

### Risk Factors Associated With OS

Univariate Cox hazards analysis showed that smoking status, BMI, histological type, pathological T stage, pathological N stage, and preoperative NLR were

**Table I** Patient Characteristics

| Variables                                  | No./Mean $\pm$ SD  |
|--|--------------------|
| Age (years)                                | 61.33 $\pm$ 13.31  |
| Gender                                     |                    |
| Male                                       | 123                |
| Female                                     | 24                 |
| Smoking status                             |                    |
| Never smoked                               | 21                 |
| Smoked in past                             | 126                |
| BMI (kg/m <sup>2</sup> )                   | 24.13 $\pm$ 3.31   |
| Tumor size                                 |                    |
| <2.5cm                                     | 89                 |
| $\geq$ 2.5cm                               | 58                 |
| Histological type                          |                    |
| Low  | 31                 |
| Medium                                     | 84                 |
| High                                       | 32                 |
| Pathological T stage                       |                    |
| T1   | 21                 |
| T2   | 61                 |
| T3   | 33                 |
| T4   | 32                 |
| Pathological N stage                       |                    |
| Negative (NX, N0)                          | 51                 |
| Positive (N1, N2, N3)                      | 96                 |
| Surgery                                    |                    |
| Endoscopic resection                       | 44                 |
| Endoscopic resection + Lateral rhinotomy   | 103                |
| Laboratory                                 |                    |
| Albumin, g/l                               | 42.32 $\pm$ 5.43   |
| Hemoglobin, g/dl                           | 127.45 $\pm$ 20.56 |
| White blood cell count, 10 <sup>9</sup> /L | 7.11 $\pm$ 2.98    |
| Neutrophil count, 10 <sup>9</sup> /L       | 4.88 $\pm$ 2.91    |
| Platelet count, 10 <sup>9</sup> /L         | 229.91 $\pm$ 74.25 |
| NLR  | 4.19 $\pm$ 1.33    |

**Abbreviations:** BMI, Body Mass Index; NLR, neutrophil to lymphocyte ratio.

associated with the OS (Table 2). However, multivariate analysis prompted only pathological T stage (HR 1.719, CI 1.277–3.642,  $p < 0.001$ ), pathological N stage (HR 1.344, 95% CI 1.015–2.776,  $p < 0.001$ ), and preoperative NLR (HR 1.579, 95% CI 1.217–3.092,  $p = 0.002$ ) have influence in OS.

### Risk Factors Associated With DFS

Univariate analysis showed that smoking status, BMI, histological type, pathological T stage, pathological

N stage, and preoperative NLR may influence DFS of SSCC (Table 3). However, results showed that only the pathological T stage (HR 1.835, 95% CI 1.141–3.132,  $p < 0.001$ ), pathological N stage (HR 1.281, 95% CI 1.169–2.476,  $p < 0.001$ ), and preoperative NLR (HR 1.688, 95% CI 1.162–3.363,  $p < 0.001$ ) have statistical significance in multivariate analysis.

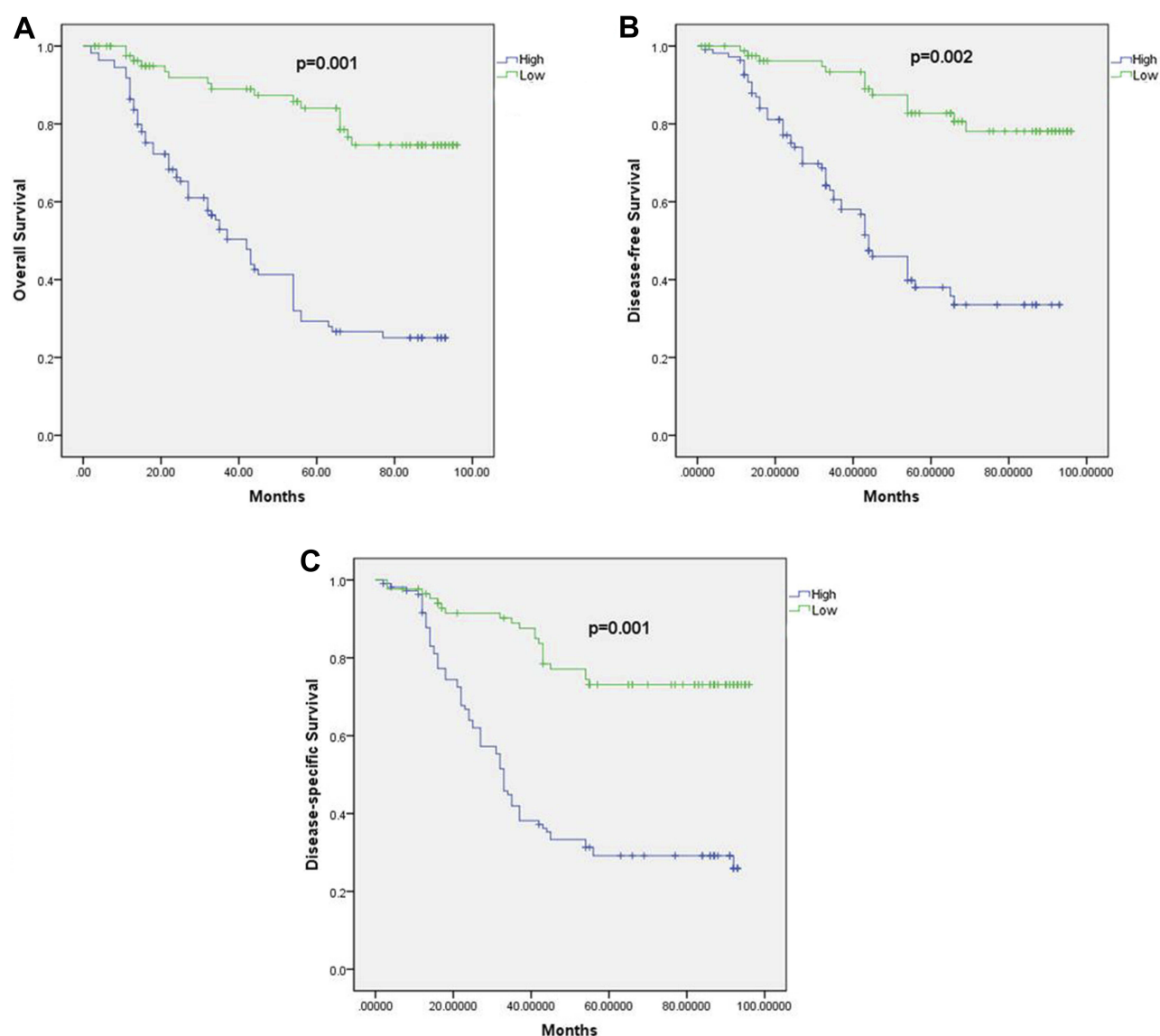
### Risk Factors Associated With DSS

Univariate analysis showed that smoking status, BMI, histological type, pathological T stage, pathological N stage, and preoperative NLR may influence DSS of SSCC (Table 4). However, results showed that only pathological T stage (HR  $p < 0.001$ , 95% CI 1.537–3.021,  $p < 0.001$ ), pathological N stage (HR 1.571, 95% CI 1.157–2.258,  $p < 0.001$ ), and preoperative NLR (HR 1.509, 95% CI 1.153–3.104,  $p = 0.001$ ) have statistical significance in multivariate analysis.

### Discussion

As cancer with a very poor prognosis, there is still no treatment that can significantly improve the survival of patients except surgical treatment.<sup>11,12</sup> It has been reported that SSCC was related to chronic stimulation such as smoking, drinking, and nutritional factors. Although surgery combined with radiotherapy and chemotherapy has been widely used, prolonging the survival of patients with SSCC remains a challenge. Many studies have found that systemic inflammatory response is closely related to the prognosis of patients with various tumors including SSCC, which provides a new basis for the stratified treatment of patients.<sup>13,14</sup>

As a reliable marker of systemic inflammation, the simplicity and convenience of neutrophils and lymphocytes make them easy to detect in terms of their ability to reflect the immune state of the body.<sup>15,16</sup> The inflammatory state of the body has been shown to be closely related to pathological processes such as tumorigenesis, angiogenesis, apoptosis inhibition, and distant metastasis, especially in patients with advanced cancer, where changes in inflammatory markers are more closely related to patient survival.<sup>17–19</sup> Elevated neutrophils may activate and control tumor cell proliferation, angiogenesis, chemokines, and expression of cytokine genes. The reduction of lymphocytes is the manifestation of immune suppression, which is undoubtedly a warning of poor prognosis.<sup>17,20</sup> Separate use of neutrophils or lymphocytes can not fully reflect the body state of inflammation, immune level and



**Figure 1** OS (A), DSS (B) and DFS (C) curves of patients with high NLR versus those with low NLR.

show the progress of tumor. Considering the possible errors in the prediction of patient prognosis using the two indicators alone, NLR may be a better choice.

The inflammatory microenvironment promotes tumor growth and migration, and in turn, tumor cells facilitate the release of inflammatory factors.<sup>21,22</sup> Activation of inflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor- $\alpha$ , leads to an increase in neutrophils and lymphocytes. In recent years, many studies have looked at the effects of inflammatory markers in the blood on tumors, and the rising trend in NLR has been shown to increase the risk of death in cancer patients.<sup>23,24</sup> We used the median preoperative NLR to determine its truncation value, and the results showed

that the survival rate of patients with low preoperative NLR was significantly higher than that of patients with high preoperative NLR which consistent with previous studies. Getzler et al found that  $NLR > 2.5$  is an independent risk factor of non-muscle invasive cancer prognosis, indicating poor recurrence-free survival.<sup>25</sup> In a retrospective study of 1020 patients with hepatocellular carcinoma in Yang et al, NLR was confirmed as an independent predictor of recurrence after analysis by propensity score matching.<sup>17</sup> In addition, previous literature also indicated that  $NLR > 6.875$  was associated with the risk of distant metastasis and death in patients with palatal tonsillar squamous cell carcinoma receiving postoperative intensity modulated radiotherapy.<sup>26</sup>

**Table 2** Univariate And Multivariate Cox Hazards Analysis For OS In Patients With SSCC

| Variables  | Univariate Analysis   |  | Multivariate Analysis   |         |
|--|---|--|-------------------------|---------|
|  | HR (95% CI)   | p-value  | HR(95% CI)              | p-value |
| Age (years)<br>>58<br>≤58  | 1<br>0.339(0.132–1.627)   | 0.347  |                         |         |
| Gender<br>Male<br>Female   | 1<br>1.369(0.594–1.724)   | 0.535  |                         |         |
| Smoking status<br>Never smoked<br>Smoked in past   | 1<br>1.209(1.013–1.875)   | 0.021  | 1<br>0.935(0.285–1.941) | 0.698   |
| BMI(kg/m <sup>2</sup> )<br>≤22.45<br>>22.45  | 1<br>1.209(1.011–2.033)   | 0.011  | 1<br>0.881(0.215–1.228) | 0.588   |
| Tumor size<br>≤2.5cm<br>>2.5cm   | 1<br>1.559(0.433–3.381)   | 0.665  |                         |         |
| Histological type<br>High<br>Medium, low   | 1<br>1.756(1.553–2.663)   | 0.002  | 1<br>1.031(0.484–2.015) | 0.351   |
| Pathological T stage<br>T1, T2<br>T3, T4   | 1<br>1.669(1.353–3.664)   | <0.001   | 1<br>1.719(1.277–3.642) | <0.001  |
| Pathological N stage<br>Negative(NX, N0)<br>Positive(N1, N2, N3)   | 1<br>1.214(1.052–2.617)   | <0.001   |                         | <0.001  |
| Surgery<br>Nasal endoscopy<br>Nasal endoscopy + Lateral rhinotomy<br>Albumin(>38.3/≤38.3, g/l)<br>Hemoglobin(>128/≤128), g/dl)<br>WBC count, (>8.34/≤8.34, 10 <sup>9</sup> /L)<br>Neutrophil count, (>5.44/≤5.44, 10 <sup>9</sup> /L)<br>Platelet count, (>198/≤198, 10 <sup>9</sup> /L) | 1<br>1.570(0.255–4.114)<br>1.187(0.746–1.665)<br>0.414(0.139–1.439)<br>1.145(0.343–1.549)<br>1.975(0.644–2.988)<br>1.804(0.773–2.191) | 0.547<br><br>0.441<br>0.571<br>0.648<br>0.773<br>0.761 |                         |         |
| NLR<br>High (≤4.25)<br>Low(>4.25)  | 1<br>1.888(1.336–3.342)   | <0.001   | 1<br>1.579(1.217–3.092) | 0.002   |

**Abbreviations:** BMI, Body Mass Index; NLR, neutrophil to lymphocyte ratio.

NLR is a known systemic inflammatory scoring system that plays an important role in systemic inflammation and immune response in tumor growth.<sup>27,28</sup> Although the predictive value of NLR has been reported in many tumors, its potential mechanism as a prognostic factor remains to be further studied.<sup>29</sup> In fact, many blood markers have been linked to aggressive and

metastatic tumors. As a marker of inflammatory response, NLR is also related to tumor proliferation, invasion, metastasis and drug resistance.<sup>30</sup> Yoshida et al found that the function of preoperative NLR in predicting disease-free survival of patients with stage I-II rectal cancer was equivalent to pathologic t-category, and lymphatic invasion, which could be an

**Table 3** Univariate And Multivariate Cox Hazards Analysis For DFS In Patients With SSCC

| Variables   | Univariate Analysis   |  | Multivariate Analysis   |         |
|---|---|--|-------------------------|---------|
|   | HR (95% CI)   | p-value  | HR (95% CI)             | p-value |
| Age (years)<br>>58<br>≤58   | 1<br>0.357(0.119–1.510)   | 0.322  |                         |         |
| Gender<br>Male<br>Female  | 1<br>1.447(0.699–1.919)   | 0.472  |                         |         |
| Smoking status<br>Never smoked<br>Smoked in past  | 1<br>1.312(1.055–1.967)   | 0.033  | 1<br>0.881(0.253–1.749) | 0.783   |
| BMI(kg/m <sup>2</sup> )<br>≤22.45<br>>22.45   | 1<br>1.371(1.075–1.939)   | 0.025  | 1<br>0.654(0.197–1.134) | 0.672   |
| Tumor size<br>≤2.5cm<br>>2.5cm  | 1<br>1.479(0.513–3.099)   | 0.588  |                         |         |
| Histological type<br>High<br>Medium, low  | 1<br>1.667(1.379–2.501)   | 0.014  | 1<br>1.266(0.571–2.233) | 0.516   |
| Pathological T stage<br>T1, T2<br>T3, T4  | 1<br>1.578(1.362–3.546)   | <0.001   | 1<br>1.835(1.141–3.132) | <0.001  |
| Pathological N stage<br>Negative(NX, N0)<br>Positive(N1, N2, N3)  | 1<br>1.365(1.141–2.388)   | <0.001   |                         | <0.001  |
| Surgery<br>Nasal endoscopy<br>Nasal endoscopy + Lateral rhinotomy<br>Albumin(>38.3/≤38.3, g/l)<br>Hemoglobin(>128/≤128, g/dl)<br>WBC count, (>8.34/≤8.34, 10 <sup>9</sup> /L)<br>Neutrophil count, (>5.44/≤5.44, 10 <sup>9</sup> /L)<br>Platelet count, (>198/≤198, 10 <sup>9</sup> /L) | 1<br>1.257(0.614–3.845)<br>1.219(0.511–1.546)<br>0.452(0.261–1.578)<br>1.274(0.215–1.659)<br>1.845(0.884–2.732)<br>1.633(0.815–2.442) | 0.589<br><br><br>0.674<br>0.615<br>0.463<br>0.547<br>0.632 |                         |         |
| NLR<br>High (≤4.25)<br>Low(>4.25)   | 1<br>1.763(1.156–3.149)   | <0.001   | 1<br>1.688(1.162–3.363) | <0.001  |

**Abbreviations:** BMI, Body Mass Index; NLR, neutrophil to lymphocyte ratio.

independent predictor of tumor recurrence.<sup>31</sup> In this study, univariate and multivariate analyses indicated that preoperative NLR was an independent predictor of poor prognosis for SSCC, whether in OS, DSS or DFS. Patients in the group with higher preoperative NLR levels had a lower five-year survival rate than those with lower preoperative NLR levels.

This study has some limitations. Firstly, this is a single-center study, which inevitably limits the number of samples. The reliability of our conclusion needs to be confirmed by future multi-center studies. Secondly, we only focused on SSCC, and whether this conclusion is applicable to most patients with head and neck tumors remains to be unclear. In addition, we have only verified

**Table 4** Univariate And Multivariate Cox Hazards Analysis For DSS In Patients With SSCC

| Variables  | Univariate Analysis  |  | Multivariate Analysis    |         |
|--|--|--|--------------------------|---------|
|  | HR (95% CI)  | p-value  | HR (95% CI)              | p-value |
| Age (years)<br>>58<br>≤58  | 1<br>0.436(0.201–1.555)  | 0.498  |                          |         |
| Gender<br>Male<br>Female   | 1<br>1.386(0.721–1.976)  | 0.562  |                          |         |
| Smoking status<br>Never smoked<br>Smoked in past   | 1<br>1.447(1.121–1.998)  | 0.027  | 1<br>0.802(0.314–1.853)  | 0.814   |
| BMI(kg/m <sup>2</sup> )<br>≤22.45<br>>22.45  | 1<br>1.435(1.028–1.953)  | 0.009  | 1<br>0.774(0.216–1.339)  | 0.737   |
| Tumor size<br>≤2.5cm<br>>2.5cm   | 1<br>1.533(0.635–3.205)  | 0.625  |                          |         |
| Histological type<br>High<br>Medium, low   | 1<br>1.582(1.246–2.672)  | 0.036  | 1<br>1.378 (0.649–2.546) | 0.671   |
| Pathological T stage<br>T1, T2<br>T3, T4   | 1<br>1.453(1.259–3.133)  | <0.001   | 1<br>1.744(1.537–3.021)  | <0.001  |
| Pathological N stage<br>Negative<br>Positive   | 1<br>1.477(1.204–2.142)  | <0.001   | 1<br>1.571(1.157–2.258)  | <0.001  |
| Surgery<br>Nasal endoscopy<br>Nasal endoscopy + Lateral rhinotomy<br>Albumin(>38.3/≤38.3, g/l)<br>Hemoglobin(>128/≤128), g/dl)<br>WBC count, (>8.34/≤8.34, 10 <sup>9</sup> /L)<br>Neutrophil count, (>5.44/≤5.44, 10 <sup>9</sup> /L)<br>Platelet count, (>198/≤198, 10 <sup>9</sup> /L) | 1<br>1.514(0.735–3.333)<br>1.646(0.621–1.879)<br>0.601(0.315–1.449)<br>1.443(0.301–1.877)<br>1.566(0.642–2.559)<br>1.753 (0.469–2.005) | 0.663<br><br>0.774<br>0.508<br>0.516<br>0.688<br>0.594 |                          |         |
| NLR<br>High (≤4.25)<br>Low(>4.25)  | 1<br>1.359(1.033–3.314)  | <0.001   | 1<br>1.509(1.153–3.104)  | 0.001   |

**Abbreviations:** BMI, Body Mass Index; NLR, neutrophil to lymphocyte ratio.

a small number of indicators in the blood, and whether other indicators can better predict the prognosis of SSCC needs to be confirmed by further studies. Moreover, high neutrophil count and low lymphocyte count can both lead to High NLR, leading to inaccurate results. Finally, this study included only patients who underwent surgery. Whether NLR is suitable for SSCC patients with other

treatments or surgery combined with other treated requires more research in the future.

In conclusion, our results suggest that preoperative NLR is associated with survival in SSCC patients. As a simple and easy to calculate inflammatory marker, the level of pre-treatment NLR could help us identify high-risk patients with SSCC.



## Ethical Approval And Informed Consent

All patients provided written informed consent, and that this was conducted in accordance with the Declaration of Helsinki. The study was approved by the ethics committee of the West China Hospital of Sichuan University.

## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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