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Preoperative neutrophil-to-lymphocyte ratio is an independent prognostic marker in patients with laryngeal squamous cell carcinoma

Xiu-Ping Tu, Qian-Hui Qiu, Liang-Si Chen, Xiao-Ning Luo, Zhong-Ming Lu, Si-Yi Zhang* and Shao-Hua Chen*

Abstract

Background: Neutrophil-lymphocyte ratio (NLR) has been shown to be associated with prognosis in various solid tumors. This study aimed to evaluate the prognostic role of NLR in patients with laryngeal squamous cell carcinoma (LSCC).

Methods: A total of 141 LSCC patients were retrospectively reviewed. Patients' demographics were analyzed along with clinical and pathologic data. The optimal cutoff value of NLR was determined using receiver operating characteristic (ROC) curve analysis. The impact of the NLR and other potential prognostic factors on disease-free survival (DFS) and overall survival (OS) was assessed using the Kaplan-Meier method and multivariate Cox regression analysis.

Results: The optimal cutoff value of the NLR was 2.17. In the NLR \leq 2.17 group, the 1-, 3-, and 5-year DFS rates were 88.2, 73.9 and 69.1 %, respectively, while in the NLR $>$ 2.17 group, the DFS rates were 83.0, 54.6 and 49.2 %, respectively. Correspondingly, the 1-, 3-, and 5-year OS rates were 98.9, 85.1 and 77.4 % in the NLR \leq 2.17 group and 97.9, 63.8 and 53.3 % in the NLR $>$ 2.17 group, respectively. The multivariate Cox proportional hazard model analysis showed that NLR $>$ 2.17 was a prognostic factor for both DFS [hazard ratio (HR) = 1.869; 95 % confidence interval (CI) 1.078–3.243; P = 0.026] and OS (HR = 2.177; 95 % CI 1.208–3.924; P = 0.010).

Conclusion: Our results showed that elevated preoperative NLR was an independent predictor of poor prognosis for patients with LSCC after surgical resection.

Keywords: Laryngeal squamous cell carcinoma, Neutrophil-lymphocyte ratio, Prognostic marker

Background

Laryngeal squamous cell carcinoma (LSCC) is one of the most common head and neck malignancies that remain as significant cause of morbidity and mortality. Approximately 650,000 new cases and 350,000 cancer deaths attributed to this condition occur every year [1, 2]. Treatment options in LSCC include surgery, radiotherapy, chemotherapy, or a combination of surgery, radio- and chemotherapy [3–7]. Despite improvements in treatment, an epidemiological survey indicated that the clinical outcome for LSCC has improved little in the past 20 years [8]. Therefore, it is of great significance to find novel and

effective biomarkers for prediction of LSCC patients with poor prognosis or at high risk of early recurrence.

Recently, there is increasing evidence that the host inflammatory response to cancer is associated with poor tumor-specific prognosis. Kawata et al. reported that lymphocyte infiltration around the tumor is associated with a better prognosis of HCC [9], whereas neutrophil in tumor stroma is associated with a poor prognosis [10]. Likewise, the neutrophil-to-lymphocyte ratio (NLR), a predictor of the patient's inflammatory status, has been shown to be an effective prognostic marker in many solid tumors [11–17]. Kum et al. showed that neutrophil-to-lymphocyte ratio elevated in squamous cell carcinoma of larynx compared to benign and precancerous laryngeal lesions [18]. To our knowledge, the prognostic value of

* Correspondence: szhang555@hotmail.com; chenshaohua1168@163.com
Department of Otorhinolaryngology, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, Guangdong 510080, P. R. China

NLR in laryngeal squamous cell carcinoma has not been reported.

In this study, we evaluated the prognostic value of pre-operative NLR in patients with LSCC after surgical resection.

Methods

Patients

Clinical data were collected from patients with LSCC who underwent surgical resection at the Department of Otorhinolaryngology, Guangdong General Hospital & Guangdong Academy of Medical Sciences from January 2006 to August 2011. Clinical stage of laryngeal cancer was determined according to the AJCC- TNM stage (7th ed, 2010) [19]. The selective criteria for the patients were as follows: (1) laryngeal squamous cell carcinoma confirmed by pathology, (2) older than 18 years of age; (3) complete clinical, laboratory, imaging, and follow-up data; (4) no evidence of sepsis [11]; (5) no hematological disorders or treatment that could result in an elevated NLR, for example, administration of hematopoietic agents such as granulocyte-colony stimulating factor (G-CSF) within 1 month before surgery; (6) no autoimmune disease or treatment with steroids; (7) no pre-operative treatments such as radiotherapy or chemotherapy; (8) patients were treated with curative intent. Routine blood tests were performed on the day before surgery. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. Patients were followed-up every 3 months for survival status, disease progression and time of death. The last follow-up was 30 September 2014. Disease-free survival (DFS) was recorded from the date of surgery to the date of recurrence, or last follow-up. Overall survival (OS) was recorded from the date of surgery to the date of death or last follow-up. This study was approved by the Research Ethics Committee of Guangdong General Hospital & Guangdong Academy of Medical Sciences. All participants signed informed consent to participate in the study.

Statistical analysis

All statistical analyses were performed with SPSS version 19.0 software (Chicago, IL, USA). The chi-square test was used to compare categorical variables. Survival curves were plotted using the Kaplan-Meier method and compared using the log-rank test. Factors analyzed by univariate analysis with $P < 0.05$ were included in multiple Cox proportional hazards model. $P < 0.05$ was considered significant.

Results

Demographic data

A total of 141 patients were eligible for the study. The median age at diagnosis was 59 (range 36–87) years.

There were 137 men and 4 women. Eighty-three patients (58.9 %, 83/141) had a smoking index of 20 pack-year or more [20], and 24 patients (17.0 %, 24/141) had a drinking index of 1000 g-year or more [21]. Surgical procedures included total laryngectomy (43 cases, 30.5 %), partial laryngectomy (64 cases, 45.4 %), and CO2 laser surgery (34 cases, 24.1 %). The locations of tumors included 80.2 % (113/141) glottic, 17.0 % (24/141) supraglottic and 2.8 % (4/141) subglottic. Most of the patients were in the N0 stage (83.7 %, 118/141), with 23 patients (16.3 %, 23/141) in the N1 to N3 stages. Eighty-six patients (61.0 %, 86/141) were in T1 to T2 stages, and 55 patients (39.0 %, 55/141) were in the T3 to T4 stages. Details of features are shown in Table 1.

Table 1 Correlation between peripheral NLR and clinicopathologic variables of LSCC patients

| Variables | Cases | NLR | | P |
|-----------------------|-------|-------------|-------------|-------|
| | | NLR ≤ 2.17 | NLR > 2.17 | |
| Age (years) | | | | |
| ≤ 60 | 74 | 48 (64.9 %) | 26 (35.1 %) | 0.633 |
| > 60 | 67 | 46 (68.7 %) | 21 (31.3 %) | |
| Sex | | | | |
| Male | 137 | 90 (65.7 %) | 47 (34.3 %) | 0.151 |
| Female | 4 | 4 (100.0 %) | 0 | |
| Smoking history | | | | |
| Yes | 83 | 54 (65.1 %) | 29 (34.9 %) | 0.628 |
| No | 58 | 40 (69.0 %) | 18 (31.0 %) | |
| Drinking history | | | | |
| Yes | 24 | 15 (62.5 %) | 9 (37.5 %) | 0.635 |
| No | 117 | 79 (67.5 %) | 38 (32.5 %) | |
| T classification | | | | |
| T1–T2 | 86 | 62 (72.1 %) | 24 (27.9 %) | 0.087 |
| T3–T4 | 55 | 32 (58.2 %) | 23 (41.2 %) | |
| Lymph node metastasis | | | | |
| Negative | 118 | 80 (67.8 %) | 38 (32.2 %) | 0.519 |
| Positive | 23 | 14 (60.9 %) | 9 (39.1 %) | |
| Histological grade | | | | |
| Well | 48 | 34 (70.8 %) | 14 (29.2 %) | 0.670 |
| Moderately | 73 | 48 (65.8 %) | 25 (34.2 %) | |
| Poorly | 20 | 12 (60.0 %) | 8 (40.0 %) | |
| Primary location | | | | |
| Supraglottic | 24 | 15 (62.5 %) | 9 (37.5 %) | 0.671 |
| Glottic | 113 | 77 (68.1 %) | 36 (31.9 %) | |
| Subglottic | 4 | 2 (50.0 %) | 2 (50.0 %) | |
| Clinical stage | | | | |
| I–II | 80 | 58 (72.5 %) | 22 (27.5 %) | 0.092 |
| III–IV | 61 | 36 (59.0 %) | 25 (41.0 %) | |

NLR neutrophil-to-lymphocyte ratio, LSCC Laryngeal squamous cell carcinoma

An optimal cutoff value for elevated NLR

To avoid a predetermined cutoff point, the optimal cutoff score of preoperative NLR was defined by receiver operating characteristic (ROC) curve analysis. The cutoff value was that point closest to both maximum sensitivity and specificity. According to the ROC curve, the optimal cutoff value of preoperative NLR was 2.17. The area under the ROC curves was 0.614 with a 95 % confidence interval (95 % CI) for the area between 0.515 and 0.713 ($P = 0.024$) (Fig. 1). Clinicopathological features according to NLR groups are summarized in Table 1.

DFS and OS according to NLR status

The 141 patients were divided into two groups: $NLR \leq 2.17$ and $NLR > 2.17$. The median patients' follow-up was 51 months (range: 5–102 months; mean \pm SD: 54.1 ± 23.4 months). Ninety-six patients were alive at the end of follow-up and 52 patients developed recurrence 5–102 months after surgery (median 46 months). In the $NLR \leq 2.17$ group, the 1-, 3-, and 5-year DFS rates were 88.2, 73.9 and 69.1 %, respectively, while in the $NLR > 2.17$ group, the DFS rates were 83.0, 54.6 and 49.2 %, respectively (Fig. 2). Correspondingly, the 1-, 3-, and 5-year OS rates were 98.9, 85.1 and 77.4 % in the $NLR \leq 2.17$ group and 97.9, 63.8 and 53.3 % in the $NLR > 2.17$ group, respectively (Fig. 3). Both DFS and OS of patients in the

$NLR \leq 2.17$ group were significantly longer than for patients in the $NLR > 2.17$ group.

Risk factors for prognosis of LSCC

For all patients included in this study, the 1-, 3- and 5-year DFS rates were 86.5, 67.5 and 62.4 %, respectively. Rates for OS at the 1-, 3- and 5-year period were 98.6, 78.0 and 69.4 %, respectively. Univariate analysis revealed that advanced T classification (T3 and T4 stages), Lymph node metastasis, primary location, $NLR > 2.17$ and advanced clinic stage were associated with significantly poor DFS. Similarly, advanced T classification, Lymph node metastasis, primary location, $NLR > 2.17$, poor histological grade and advanced clinical stage all predicted poor OS (Table 2).

Clinical stage was first excluded from the multivariable analyses because it was a comprehensive variable, and the other variables were entered stepwise into the multivariable Cox proportional hazard model by the forward conditional method. The analysis showed that $NLR > 2.17$ (HR = 1.869; 95 % CI 1.078–3.243; $P = 0.026$) and lymph node metastasis (HR = 3.224; 95 % CI 1.751–5.937; $P < 0.001$) were independent prognostic factors for DFS in patients with LSCC. $NLR > 2.17$ (HR = 2.177; 95 % CI 1.208–3.924; $P = 0.010$), lymph node metastasis (HR = 2.968; 95 % CI 1.548–5.692; $P = 0.001$) and advanced T classification (HR = 1.867; 95 % CI 1.018–3.425; $P = 0.044$) were independent prognostic factors for OS in patients with LSCC (Table 3).

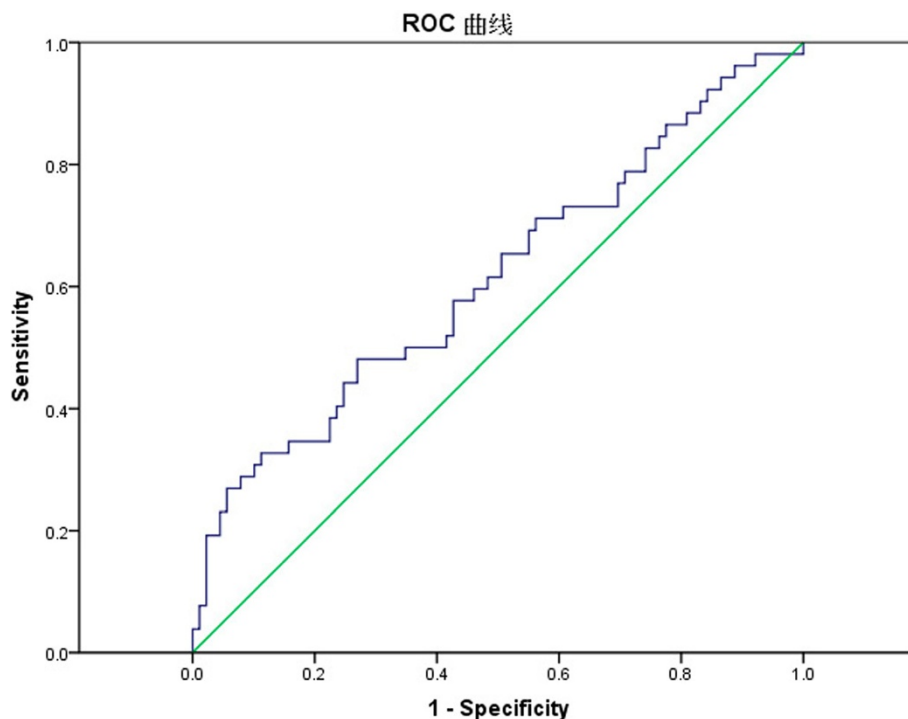


Fig. 1 Receiver operating characteristic curves of preoperative neutrophil-to-lymphocyte ratio (NLR) for predicting tumor recurrence in patients with Laryngeal squamous cell carcinoma (LSCC) after surgical resection

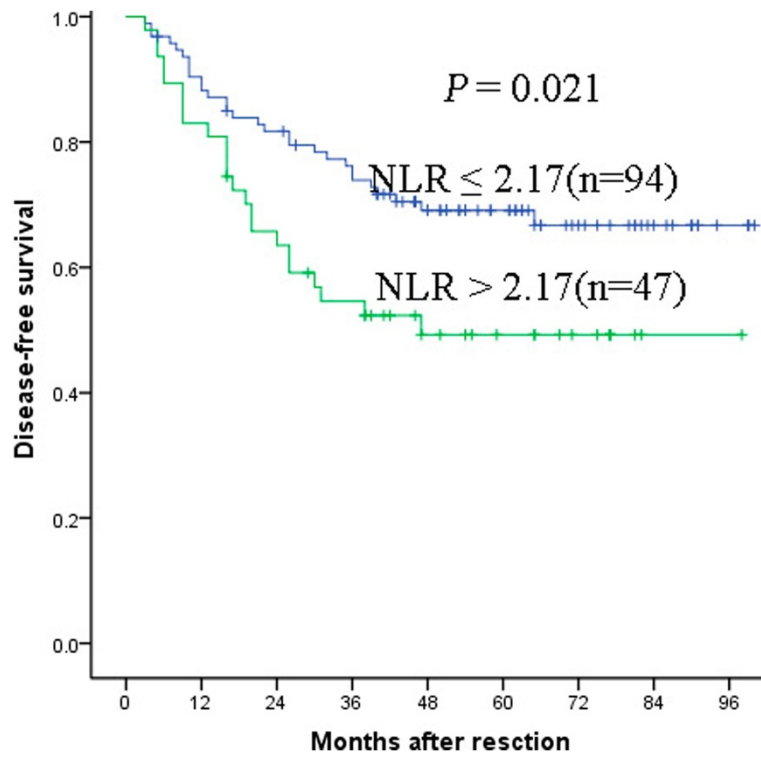


Fig. 2 Kaplan-Meier survival curves for DFS in patients with LSCC after surgical resection. Disease-free survival of patients with NLR > 2.17 was shorter than those with NLR ≤ 2.17 ($P = 0.021$, log-rank)

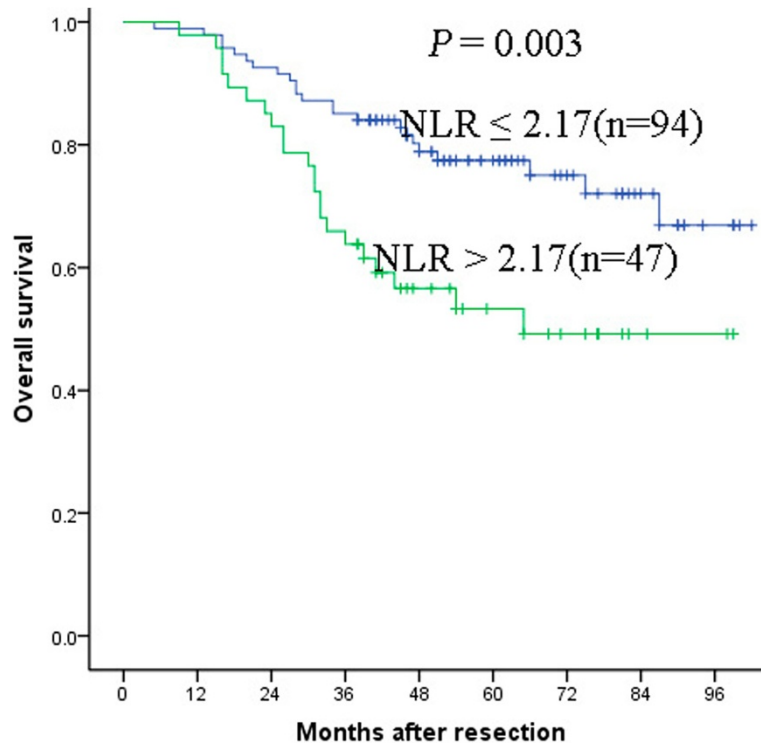


Fig. 3 Kaplan-Meier survival curves for OS in patients with LSCC after surgical resection. Overall survival of patients with NLR > 2.17 was also shorter than those with NLR ≤ 2.17 ($P = 0.003$, log-rank)

Table 2 Prognostic factors for DFS and OS by univariate analysis

| Variables | n | DFS | | | OS | | |
|-----------------------|-----|---------|---------|--------|---------|---------|--------|
| | | 3-years | 5-years | P | 3-years | 5-years | P |
| Age (years) | | | | | | | |
| ≤ 60 | 74 | 65.6 % | 64.1 % | | 75.7 % | 72.7 % | |
| > 60 | 67 | 69.4 % | 60.7 % | 0.980 | 80.6 % | 66.9 % | 0.41 |
| Smoking history | | | | | | | |
| Yes | 83 | 68.3 % | 62.7 % | | 74.7 % | 67.2 % | |
| No | 58 | 66.3 % | 62.2 % | 0.886 | 82.8 % | 73.0 % | 0.464 |
| Drinking history | | | | | | | |
| Yes | 24 | 66.4 % | 61.7 % | | 66.7 % | 61.1 % | |
| No | 117 | 67.7 % | 62.6 % | 0.845 | 80.3 % | 71.1 % | 0.414 |
| T classification | | | | | | | |
| T1–T2 | 86 | 74.3 % | 68.6 % | | 87.2 % | 79.6 % | |
| T3–T4 | 55 | 56.1 % | 51.8 % | 0.039 | 63.6 % | 53.7 % | 0.003 |
| Lymph node metastasis | | | | | | | |
| Negative | 118 | 73.3 % | 68.4 % | | 83.9 % | 75.9 % | |
| Positive | 23 | 35.5 % | 28.4 % | <0.001 | 47.8 % | 35.9 % | <0.001 |
| NLR | | | | | | | |
| ≤ 2.17 | 94 | 73.9 % | 69.1 % | | 85.1 % | 77.4 % | |
| > 2.17 | 47 | 54.6 % | 49.2 % | 0.021 | 63.8 % | 53.3 % | 0.003 |
| Histological grade | | | | | | | |
| Well | 48 | 83.0 % | 70.5 % | | 93.7 % | 80.4 % | |
| Moderately | 73 | 59.6 % | 59.6 % | | 74.0 % | 67.4 % | |
| Poorly | 20 | 59.6 % | 53.6 % | 0.169 | 55.0 % | 49.5 % | 0.043 |
| Primary location | | | | | | | |
| Supraglottic | 24 | 55.9 % | 43.1 % | | 58.3 % | 37.4 % | |
| Glottic | 113 | 69.5 % | 66.6 % | | 82.3 % | 77.4 % | |
| Subglottic | 4 | 75.0 % | 50.0 % | 0.165 | 75.0 % | 50.0 % | 0.001 |
| Clinical stage | | | | | | | |
| I–II | 80 | 74.9 % | 70.3 % | | 87.5 % | 81.1 % | |
| III–IV | 61 | 57.2 % | 51.4 % | 0.022 | 65.6 % | 54.5 % | 0.004 |

DFS disease-free survival, OS overall survival. Other abbreviations are the same as in Table 1

Discussion

Recent evidence suggests that the development and progression of cancers is closely associated with inflammation and immunity status. The neutrophil-to-lymphocyte ratio is a simple and effective marker of inflammation and immunity. It reflects the patient's inflammatory and

immunity status. NLR has been shown to be a valuable prognostic marker in patients with some solid tumors in many studies, such as hepatocellular carcinoma [11, 22], gastric cancer [23], soft tissue sarcoma [24], esophageal cancer [17, 25] and breast cancer [26, 27]. However, the cutoff value of NLR is not consistent. In most studies,

Table 3 Prognostic factors for DFS and OS as determined by multivariate Cox proportional hazards regression model

| Variables | DFS | | | OS | | |
|-----------------------|-------|-------------|--------|-------|-------------|-------|
| | HR | 95 % CI | P | HR | 95 % CI | P |
| T classification | | | | 1.867 | 1.018–3.425 | 0.044 |
| Lymph node metastasis | 3.224 | 1.751–5.937 | <0.001 | 2.968 | 1.548–5.692 | 0.001 |
| NLR | 1.869 | 1.078–3.243 | 0.026 | 2.177 | 1.208–3.924 | 0.010 |

HR hazard ratio, CI confidence interval. Other abbreviations are the same as in Tables 1 and 2

the cutoff value of NLR has been empirically set. To avoid a predetermined cutoff point, we determined that the optimal cutoff value of NLR was 2.17 for predicting prognosis of patients with LSCC by using ROC curve analysis in this study. To the best of our knowledge, this study is the first to evaluate the prognostic role of NLR in patients with LSCC.

We found that patients with elevated NLR (>2.17) had significantly shorter DFS and OS than those with low NLR (≤ 2.17) (Figs. 2 and 3, Table 2). The multiple Cox proportional hazard regression analysis showed that NLR > 2.17 was an independent prognostic factor of short DFS and OS in patients with LSCC. The relationship between a high pretreatment NLR and poor prognosis has also been observed in patients with other squamous cell carcinoma [17, 25, 28, 29]. Recently, Kum et al. demonstrated that NLR was a useful inflammatory marker to differentiate LSCC patients from benign laryngeal lesion (BLL) and precancerous laryngeal lesion (PLL) patients [18].

Although the association between elevated NLR and poor prognosis has been confirmed by many studies, the underlying mechanisms have not yet been fully elucidated [11–16]. One possible explanation is that a relatively increased number of circulating neutrophils produced and secreted angiogenesis-regulating growth factors, chemokines and proteases (e.g., vascular endothelial growth factor (VEGF) [30], interleukin-8 (IL-8) [31], intercellular adhesion molecule 1 [32] and matrix metalloproteinase (MMP)) [33] which may promote tumor growth and metastasis resulting in poor prognosis. Another explanation is that the host immune response to tumors is lymphocyte dependent. Patients with elevated NLR usually have relative lymphocytopenia, and this may reflect a deficient immune response to tumors mediated by CD4⁺ T-helper and cytotoxic CD8⁺ cell [34].

Conclusions

This study demonstrated that elevated preoperative NLR was an independent prognostic marker of poor DFS and OS in patients with LSCC. NLR is a simple, easily accessible indicator for identifying LSCC patients following surgical resection. It might help clinicians support intensive follow-up surveillance and adopt personalized adjuvant therapies for patients with LSCC who were at high risk for recurrence after surgical resection. It is noted that this study is limited by its retrospective nature and the relatively small size in a single-center. Further multicenter, large prospective studies are needed to confirm the findings.

Abbreviations

NLR: Neutrophil-lymphocyte ratio; LSCC: Laryngeal squamous cell carcinoma; ROC: Receiver operating characteristic; DFS: Disease-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; G-CSF: Granulocyte-colony stimulating factor; BLL: Benign laryngeal lesion; PLL: Precancerous laryngeal lesion; VEGF: Vascular endothelial growth factor; IL-8: Interleukin-8; MMP: Matrix metalloproteinase.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

XPT, SYZ and SHC were the main authors of the manuscript. They were involved in the conception, design and coordination of the study as well as in data analysis, interpretation of results and drafting the manuscript. SHC and SYZ were in charge of all experimental procedures. QHQ, LSC, XNL and ZML participated in the experimental procedures and revised critically the content of the manuscript. All authors contributed to the interpretation of data and critically revised the manuscript. All authors read and approved the final manuscript.

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