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HEAD AND NECK

Neutrophil-to-lymphocyte ratio as a prognostic marker for head and neck cancer with lung metastasis: a retrospective study

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Abstract

Purpose The neutrophil-to-lymphocyte ratio (NLR) is the most widely biomarker used to assess the inflammatory system in various solid cancers. An elevated NLR has been reported to be associated with worse outcomes in head and neck squamous cell cancers (HNSCC). However, questions remain about the prognostic value of these findings in HNSCC patients with lung metastasis. This study aims to quantify the prognostic impact of NLR on HNSCC patients with lung metastasis.

Methods A retrospective chart review of 169 HNSCC patients was performed at the Otorhinolaryngology and the Stomatology and Maxillofacial Surgery Department (Saint-Pierre Hospital), between 2000 and 2017. All patients were divided into two subgroups. Patients who developed lung involvement were assigned to the lung-metastasis-group (LM-group) in contrast to no-lung-metastasis-group patients (NLM-group). The prognostic significance of NLR was evaluated using multivariable analysis adjusting for overall-survival (OS) and lung-metastasis-free-survival (LMFS).

Results 95 patients were enrolled in the NLM-group while 74 were in the LM-group. Multivariable analysis highlights that patients with a higher NLR value had shortened OS in the NLM subgroup (HR 1.3; $p=0.024$). However, this association was not found in the LM subgroup. When considering both subgroups, an elevated NLR was reported as a prognostic factor of poor LMFS (HR 1.65; $p=0.047$).

Conclusion Our data revealed that pretreatment NLR is an independent prognostic factor of mortality and lung metastasis development. However, the prognostic value of NLR is not confirmed in patients who suffered from lung metastasis. Physicians should integrate these findings in their treatment algorithm approach.

Level of evidence 4

Keywords NLR · Neutrophil-to-lymphocyte ratio · Head and neck cancer · Prognostic biomarkers

Introduction

Head and neck carcinoma (HNC) is one of the sixth most common type of cancer worldwide, with more than 90% of these being head and neck squamous cell carcinoma (HNSCC). At present, 600,000 cases and 380,000 deaths

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annually worldwide are due to HNSCC [1]. The main risk factors are tobacco and alcohol habits acting separately or synergistically and the coinfection of high-risk human papilloma virus (HPV) strains including HPV 16, 18, 31, 33, and 45 [2].

The main therapeutic options for HNSCC include surgery, radiation therapy and/or chemotherapy. Unfortunately, the response to cancer treatments varies from patient to patient and a large proportion of patients will develop local and/or regional recurrence and distant metastases [3]. Despite advances in treatment, the 5-year survival rate remains low and have not improved considerably in recent years [4].

The lack of an accurate system to predict response to surgery and/or chemoradiation of individual cancer lesions has prompted us to investigate the substantial roles of neutrophils in cancer progression. Recently, previous reports demonstrated the prognostic impact of the pretreatment neutrophil-to-lymphocyte ratio (NLR) in various types of solid cancers such as esophageal cancer [5], gastric cancer [6], colorectal cancer [7], and metastatic cancers [8], reporting a more favorable overall survival (OS) in low pretreatment NLR patients.

The neutrophil-to-lymphocyte ratio (NLR) is the most widely adopted to accurately evaluate the inflammatory system, especially because it is easily calculated based on a routine laboratory test [9]. Many studies investigated the role of inflammatory markers to emphasize their significant impact on outcomes in HNSCC. The existing ones have strongly demonstrated that HNSCC tends to be more aggressive when the NLR was higher [10]. Moreover, a systematic review conducted by Mascarella et al. reported that an elevated NLR is associated with poorer OS in HNSCC patients [11]. Therefore, the NLR has emerged as a substantial marker that can be used as a pre-therapeutical prognostic tool [12].

However, to date, the tumorigenic pathway underlying the relationship between the NLR and the prognosis in HNSCC has not been clearly explained. Lymphocytes are suspected to play a major role in the tumor defense system and induce cytotoxic cell death and inhibition of tumor cell proliferation and migration. In contrast, neutrophils have the ability of reducing lymphocytes or natural killer cells activity and could enhance tumor growth [10, 13].

In addition to NLR, other inflammatory markers such as platelet-to-lymphocyte ratio (PLR), neutrophils, platelets, and monocytes counts have been shown to be significantly correlated with overall survival and disease free survival [14].

However, questions remain about the prognostic value of these findings in HNSCC patients with lung metastasis. To our knowledge, no studies investigated the role of these inflammatory cell markers in HNSCC patients with lung metastasis. As the results are still controversial, the purpose of this study was to quantify the prognostic impact of NLR on HNSCC patients with lung metastasis.

Materials and methods

Methodology of the literature review

A systematic literature review was conducted on the following databases: Medline/PubMED, Scopus, Ovid and Cochrane. MESH terms included "Head and Neck Neoplasms" AND "Lymphocytes" OR "Neutrophils" OR "Biomarkers". Studies were selected based on the subsequent criteria: patients with head and neck cancers, > 18 years, treated with radiotherapy, chemotherapy, or surgery, with at least hematological tests investigation. We excluded papers that are not written in English, abstracts without full text, and oral presentations.

Study population

This retrospective study was performed at the Otorhinolaryngology and the Stomatology and Maxillofacial (head and neck) Surgery Department (Saint-Pierre Hospital). The present study was approved by the Ethics Committee of CHU Saint Pierre (No. CE/20-09-05). Clinical data of HNSCC patients were analyzed retrospectively, in accordance with the STROBE guidelines. Patients with histologically confirmed HNSCC, treated between 2000 and 2017 were identified. Patients were included if a complete blood count (CBC) was carried out the month before the start of treatment. Inaccurate CBC due to inflammatory syndrome, concurrent infection, long-term immunosuppressive medications, synchronous active malignant tumors, thyroid, hematologic, or salivary diseases, and insufficient clinical data were considered as exclusion criteria. Blood samples were analyzed at the Saint Pierre Hospital laboratories (Table 1). Upon review of these criteria, 169 patients were included in the study (Fig. 1).

Clinical and biological characteristics

Using paper and electronic records from Saint-Pierre hospital database, clinical characteristics such as age, gender, alcohol (more than 2 drinks per day if female—more than 3 drinks per day if male) or tobacco (more than 20 pack-year) use, TNM stage, and tumor site were extracted before treatment. Clinical tumor staging was established in accordance with the eighth American Joint Committee on Cancer (AJCC) staging manual. Complete physical examination, Computed Tomography Scan (CT-scan) and Magnetic Resonance Imaging (MRI) of the head and

Table 1 Patient characteristics based on lung metastasis status

Variable	*n* (%)—mean (SD)	Lung metastasis, *n* (%)—mean (SD)		*p* value
	Total	With (LM-group)	Without (NLM-group)	
Total number of patients	169 (100)	74	95	
Age (years)	61.49 (12.3)	61.2 (11.03)	61.8 (13.26)	NS
Gender				NS
M	132 (78.1)	63 (85.1)	69 (72.6)	
F	37 (21.9)	11 (14.9)	26 (27.4)	
Alcohol use				**0.005**
Yes	80 (47.3)	26 (35.1)	54 (56.8)	
No	89 (52.7)	48 (65.9)	41 (43.2)	
Tobacco use				NS
Yes	144 (85.2)	61 (82.4)	83 (87.4)	
No	25 (14.8)	13 (17.6)	12 (12.6)	
Localization				**0.0013**
Nasopharynx	10 (5.9)	2 (2.7)	8 (8.4)	
Oropharynx	35 (20.7)	16 (21.6)	19 (20.0)	
Hypopharynx	23 (13.6)	18 (24.3)	5 (5.3)	
Larynx	43 (25.5)	16 (21.6)	27 (28.4)	
Oral cavity	55 (32.6)	19 (25.7)	36 (37.9)	
Unknown	3 (1.8)	3 (4.1)	0 (0.0)	
T status				**0.049**
T1, T2	69 (40.8)	24 (32.4)	45 (47.4)	
T3, T4	100 (59.2)	50 (67.6)	50 (52.6)	
N status				**0.039**
N0, N1	86 (50.9)	31 (41.9)	55 (57.9)	
N2, N3	83 (49.1)	43 (58.1)	40 (42.1)	
Treatment				NS
Surgical resection only	16 (9.5)	4 (5.4)	12 (12.6)	
CT and/or RT (CT-RT)	74 (43.8)	28 (37.8)	46 (48.4)	
Surgery + (CT-RT)	78 (46.2)	41 (55.4)	37 (38.9)	
No treatment	1 (0.5)	1 (1.4)	0 (0.0)	
NLR at diagnosis		3.5 (1.7)	2.72 (1.36)	**0.001**

Data written in boldface mean that *p* values were statistically significant

SD standard deviation, *NLM* no-lung metastasis, *LM* Lung Metastasis, *F* Female, *M* Male, *CT* Chemotherapy, *RT* Radiotherapy and *NLR* neutrophil-to-lymphocyte ratio

neck, thoraco-abdominal CT, PET-scan, and endoscopic examination of the upper aerodigestive tract were also performed.

Considering the hematologic parameters, lymphocyte and neutrophil levels were arranged to generate the neutrophil-to-lymphocyte ratio (NLR) as prognostic marker. In this respect, NLR was measured at diagnosis by dividing the number of neutrophils (10^3/µl) by the number of lymphocytes (10^3/µl). The cutoff value of NLR for overall survival (OS) and lung metastasis free survival (LMFS) analysis was determined by the use of the X-tile bioinformatic software (Yale University) [15]. The predetermined values (Fig. 2) were subsequently used to stratify patients into high or low NLR subgroups.

Treatment and follow-up

Treatment modalities were divided whether they had primary site surgical resection only, chemotherapy and/or radiotherapy (CT-RT), combined surgical resection and CT-RT, or no treatment.

Overall-survival (OS) was defined as the interval between diagnosis and either death or the last follow-up. Lung-metastasis-free-survival (LMFS) was calculated in patients who developed HNSCC-lung metastasis and defined as the interval between diagnosis and lung metastasis. Subsequently, the patients who developed metachronous or synchronous lung involvement were assigned to the lung-metastasis group (LM-group) in contrast to no-lung-metastasis group patients

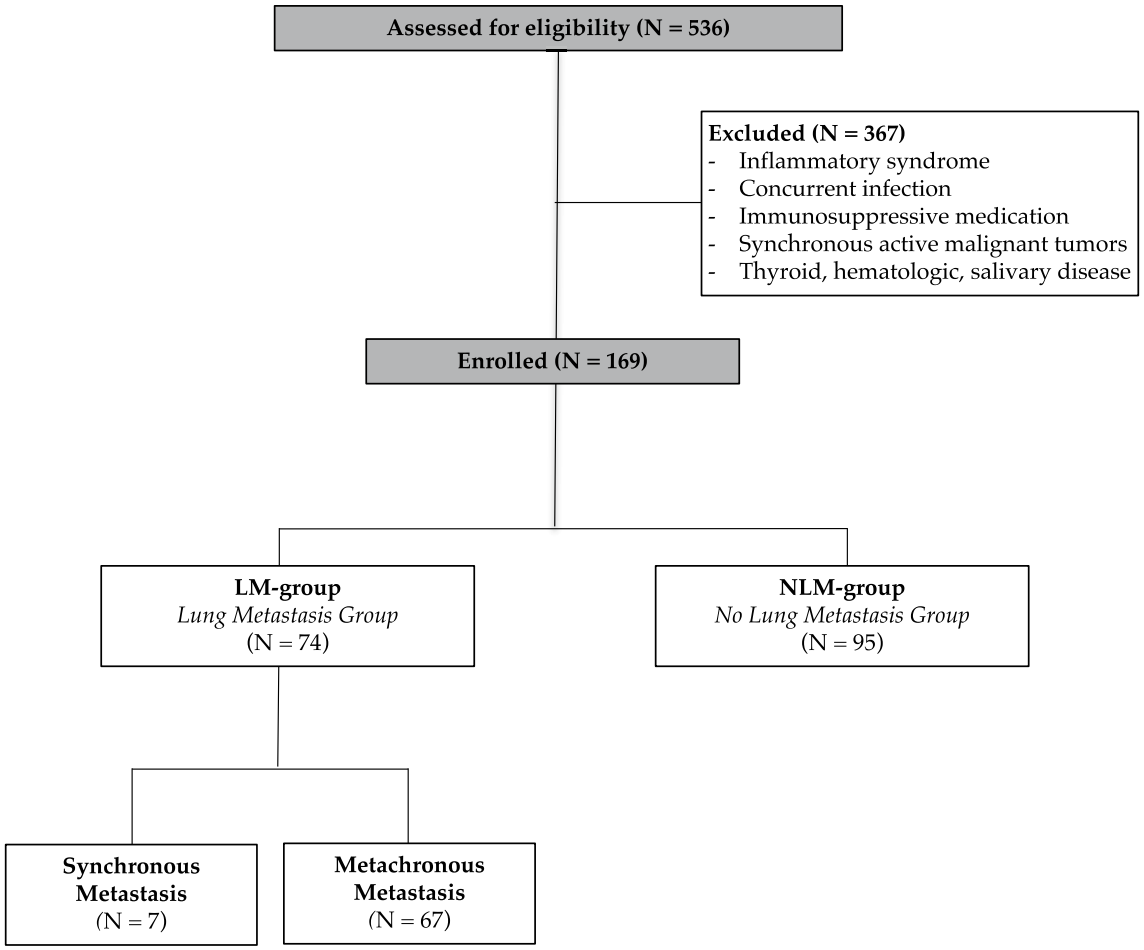

Fig.1 Diagram documenting the selection process of the 169 patients analyzed in this study

(NLM-group). Concerning the LM-group, NLR was measured again at time of lung metastasis.

Statistical analysis

Descriptive statistics (such as age, sex, alcohol and tobacco use, TNM staging) are summarized using numbers and percentages. Regarding continuous variables, means with standard deviation (SD) and medians with interquartile range (IQR) were presented for statistical analysis. The Shapiro–Wilk test was used to detect significant deviation from normality when continuous variables were used. To evaluate differences between the two groups (LM-group and NLM-group), Student's *t* test, Mann–Whitney test, Chi-squared test or Fisher's exact test were performed as appropriate.

The univariate and multivariable Cox regression analysis (using the forward stepwise regression) were conducted to assess the association between pre-therapeutic variables and OS or LMFS. Hence, continuous variables were transformed into binary variables, using the X-tile bioinformatic software to set cutoff values. In addition, effects of NLR on OS and LMFS was estimated using the Kaplan Meier survival curves and the Log-rank test.

Statistical tests were carried out using the IBM® SPSS® Statistics software. All reported *p* values are two-tailed and were considered to be significant when less than 0.05.

Results

Patient characteristics

During the follow-up, 23 patients were lost to follow-up, 89 patients died for HNSCC, and 57 patients were still alive. Among them, 95 (56.2%) patients were enrolled in the NLM-group while 74 (43.8%) were in the LM-group. The NLR values at diagnosis are available for all patients, whereas 17 NLR values at time of lung metastasis among the LM-group are missing. The demographic, clinical and treatment characteristics from these two independent groups are listed in Table 1. In our study, the majority of the patients were male in both groups (72.6% and 85.1%)

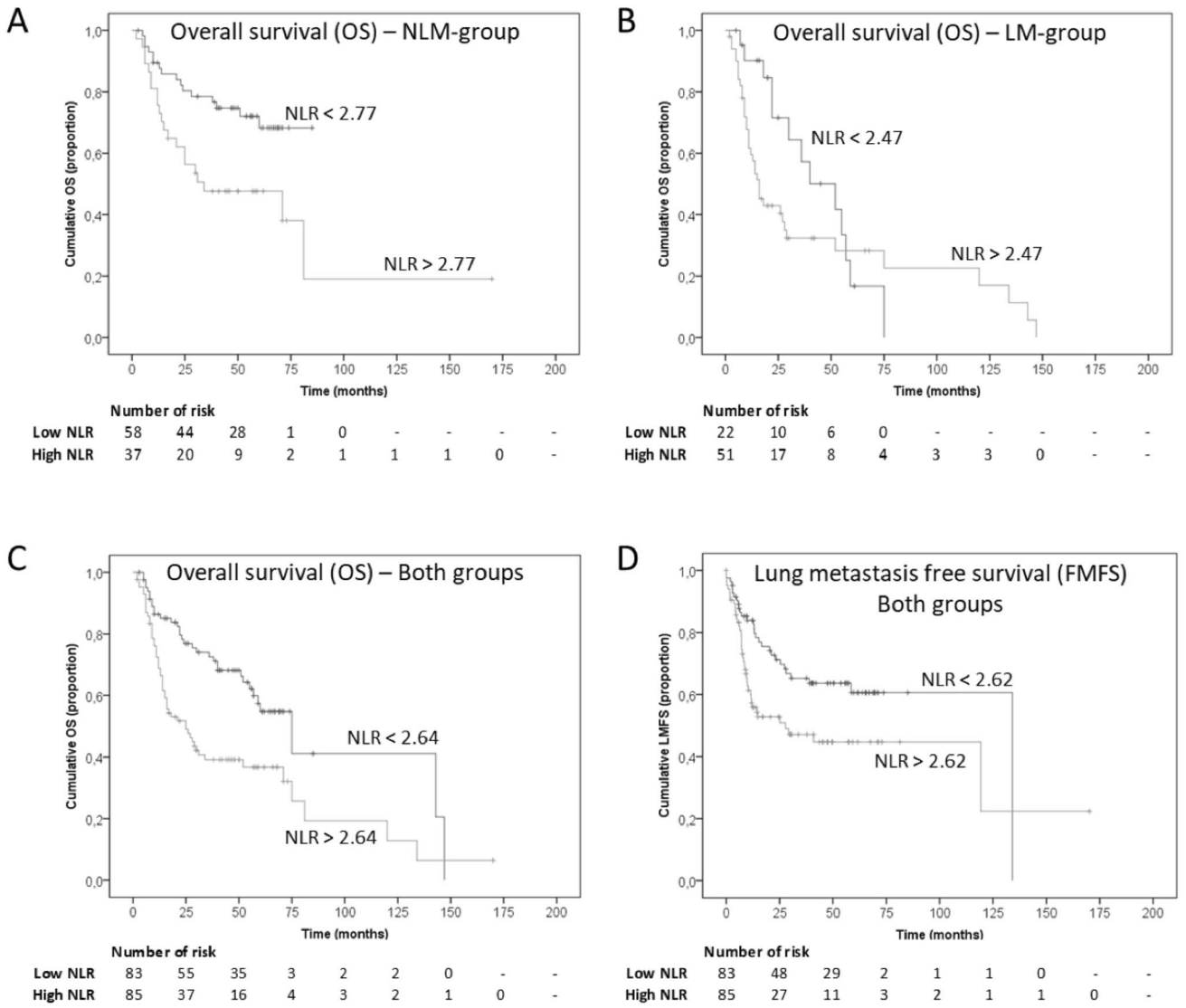

Fig. 2 **A** Association of Neutrophil-to-lymphocyte ratio to OS in the no-lung-metastasis group: Kaplan Meier curves for overall survival (OS) ($p=0.009$) comparing patients with NLR > 2.77 to NLR < 2.77 in the no-lung-metastasis group. **B** Association of Neutrophil-to-lymphocyte ratio to OS in the Lung-Metastasis Group: Kaplan Meier curves for Overall Survival (OS) ($p=0.214$) comparing patients with NLR > 2.47 to NLR < 2.47 in the Lung-Metastasis Group. **C** Association of Neutrophil-to-lymphocyte ratio to OS in both groups: Kaplan Meier curves for Overall Survival (OS) ($p=0.001$) comparing patients with NLR > 2.64 to NLR < 2.64 in both groups. **D** Association of Neutrophil-to-lymphocyte ratio to LMFS in both groups: Kaplan Meier curves for Lung Metastasis Free Survival (LMFS) ($p=0.014$) comparing patients with NLR > 2.62 to NLR < 2.62 in both groups *NLR* neutrophil-to-lymphocyte ratio, *OS* overall survival, *LMFS* lung metastasis free survival

and the median age at diagnosis was 61.8 and 61.2 years, in the NLM-group and the LM-group, respectively ($p=0.75$). Current and ex-smokers were comparable in both cohorts (87.4% and 82.4%) but alcohol use was more frequent in the NLM-group (56.8% and 35.1%) ($p=0.005$). Regarding the site of primary cancer, hypopharyngeal localization was significantly more associated with lung metastasis development ($p=0.0013$). Patients with lung metastasis tended to have a more advanced clinical T and N status at diagnosis ($p=0.049$ and 0.039, respectively). Regarding the management of the primary tumor, no difference was found between the groups in terms of treatment. In addition, we reported a significant association between NLR and lung metastasis development ($p=0.001$).

Identification of cutoff values for NLR

The mean NLR levels at diagnosis were, respectively, 3.5 and 2.7 in the LM and NLM-groups. The optimal cutoff values defined are represented in Table 2. The predetermined

Table 2 Identification of optimal cutoff values for NLR

	Groups (*n*)	Cutoff value	< *n* (%) vs > *n* (%)
NLR for OS	NLM-group (95)	2.77	59 (62.1%) vs 36 (37.9%)
NLR for OS	LM-group (74)	2.47	22 (29.7%) vs 52 (70.3%)
NLR for OS	NLM and LM groups (169)	2.64	83 (49.1%) vs 86 (50.9%)
NLR for LMFS	NLM and LM groups (169)	2.62	83 (49.1%) vs 86 (50.9%)

OS overall survival, *LMFS* lung-metastasis-free survival, *NLR* neutrophil-to-lymphocyte ratio, *NLM* no-lung metastasis, *LM* lung metastasis

values were used to stratify patients into high or low NLR subgroups.

Univariate and multivariable analysis of prognostic factors

We performed univariate and multivariable Cox-regression analysis to identify prognostic factors of OS. In the NLM-group (Table 3), univariate analysis revealed that older age, advanced T and N status, and high NLR were significantly associated to poor OS. After multivariable analysis, older age, advanced T status and higher NLR (HR 1.295; $p = 0.024$) remained statistically significant. In contrast, neither the NLR at diagnosis nor the NLR at time of lung metastasis did not seem to be associated with poor OS when lung metastasis was present. Only gender was considered as a significant predictor of OS (Table 4).

Concerning the prognostic factors of LMFS (Table 5), univariate analysis demonstrated a strong association between lung metastasis development and alcohol use, advanced T, N status, and high NLR. However, multivariable final model analysis revealed that high NLR (HR 1.65; $p = 0.047$) is the only prognostic factor of poor LMFS.

Overall survival and lung metastasis free survival

Our patients were followed with a median of 29.5 months (range 12.5–57.5 months). After stratifying as high or low NLR subgroups, log-rank survival analysis were performed and Kaplan–Meier curves were plotted. NLM-patients with high NLR (> 2.77) had poorer OS rates ($p = 0.009$) (Fig. 2A). In presence of lung metastasis (LM-group), a higher NLR (> 2.47) was not significantly associated with a difference in terms of 5-year OS (Fig. 2B). Considering both groups (NLM and LM-groups), LMFS and OS were significantly worse when a higher NLR ($p = 0.014$ and $p = 0.001$, respectively) was compared to a lower one regarding respective cutoffs (> 2.62 and > 2.64) (Fig. 2C, D).

Table 3 Univariate and multivariable cox regression analysis for overall survival in no-lung-metastasis group

Variables	Univariate analysis			Multivariable analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.09	1.01–1.07	**0.007**	1.05	1.02–1.08	**0.003**
Sex	1.16	0.57–2.34	NS	–	–	–
Alcohol use	1.54	0.78–3.03	NS	–	–	–
Tobacco use	1.02	0.4–2.64	NS	–	–	–
T status	3.07	1.48–6.36	**0.003**	3.5	1.58–7.77	**0.002**
T1–T2						
T3–T4						
N status	2.29	1.18–4.45	**0.015**	1.76	0.86–3.6	NS
N0–N1						
N2–N3						
Treatment	1.10	0.67–1.82	NS	–	–	–
Surgical resection only						
CT-RT						
Surgery + (CT-RT)						
NLR at diagnosis (> 2.77)	2.39	1.24–4.61	**0.009**	1.3	1.04–1.62	**0.024**

Data written in boldface mean that P values were statistically significant

CT Chemotherapy, *RT* Radiotherapy, *NLR* neutrophil-to-lymphocyte ratio, *HR* hazard ratio, *CI* confidence interval

Table 4 Univariate and multivariable cox regression analysis for overall survival in lung-metastasis group

Variables	Univariate analysis			Multivariable analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.02	0.99–1.04	NS	–	–	–
Sex	2.06	1.02–4.16	**0.043**	2.06	1.02–4.16	**0.043**
Alcohol use	1.74	0.99–3.05	NS	–	–	–
Tobacco use	1.14	0.52–2.47	NS	–	–	–
T status	1.358	0.75–2.46	NS	–	–	–
T1–T2						
T3–T4						
N status	1.49	0.84–2.64	NS	–	–	–
N0–N1						
N2–N3						
Treatment	1.15	0.74–1.78	NS	–	–	–
Surgical resection only						
CT-RT						
Surgery + (CT-RT)						
No treatment						
NLR at diagnosis (> 2.47)	1.50	0.79–2.86	NS	–	–	–
NLR at metastasis	1.03	0.93–1.14	NS	–	–	–

Data written in boldface mean that P values were statistically significant

CT chemotherapy, *RT* radiotherapy, *NLR* neutrophil-to-lymphocyte ratio, *HR* hazard ratio, *CI* confidence interval

Table 5 Univariate and multivariable cox regression analysis for lung metastasis free survival

Variables	Univariate analysis			Multivariable analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.01	0.98–1.03	0.396	–	–	–
Sex	0.66	0.34–1.25	0.199	–	–	–
Alcohol use	0.61	0.38–0.99	**0.043**	0.61	0.34–1.02	NS
Tobacco use	0.68	0.37–1.25	0.212	–	–	–
T status	1.85	1.13–3.03	**0.014**	1.56	0.94–2.6	NS
T1–T2						
T3–T4						
N status	1.78	1.11–2.85	**0.017**	1.43	0.88–2.32	NS
N0–N1						
N2–N3						
Treatment	1.34	0.93–1.93	0.115	–	–	–
Surgical resection only						
CT-RT						
Surgery + (CT-RT)						
No treatment						
NLR at diagnosis (> 2.62)	1.82	1.13–2.93	**0.014**	1.65	1.01–2.7	**0.047**

Data written in boldface mean that *p* values were statistically significant

CT chemotherapy, *RT* radiotherapy, *NLR* neutrophil-to-lymphocyte ratio, *HR* hazard ratio, *CI* Confidence Interval

Discussion

Nowadays, the absence of well-established biomarkers in head and neck cancers (HNC) prompted many authors to investigate effective prognostic markers [10]. Among these, the NLR seems to be of importance to better patient stratification and clinical decision [16]. Furthermore, the NLR is an easily and frequently ratio that is routinely obtained based on a blood sample [17].

Fu et al., described that a lower NLR level may be a predictor of favorable OS and better response rates, whereas an increased NLR is associated with poorer outcomes. These results were highly supported by other authors [17, 18]. Therefore, NLR is considered as a useful prognostic factor with the same value as the N status [19].

However, to this day the association between a high NLR and poor outcomes is not obviously defined in patients presenting lung metastasis.

In the current study, the following NLR cutoff values had been defined: 2.77; 2.47; 2.62; 2.64 for NLM-group, LM-group, and both groups, respectively, and are comparable to those described in the literature [14, 20]. We believe that the values reported in our analysis are cancer-specific and rely on various factors such as etiological and clinical characteristics, immunological factors [21]. Therefore, the optimal cutoff value needs to be validated in a larger population.

In the NLM-group defined in our study, we reported that factors as advanced age, advanced T status (T3–T4) and a higher NLR were significantly associated with poor OS. Moreover, after survival analyses, the patients with NLR > 2.77 had worse 5 year-OS. These findings are in concordance with the results published by Chol et al. [10]. In their retrospective study of 621 HNSCC patients treated with radiotherapy, advanced age, hypopharyngeal localization, advanced T status (T3–T4), high NLR were associated with poorer OS. Moreover, same associations were also reported by other authors concluding that preoperative NLR is an independent factor in predicting the prognosis of oral and laryngeal squamous cell carcinoma treated with surgery [22, 23]. These results are supported by prospective studies reported in the literature [24].

Interestingly, in the LM-group, the results reported in our study highlighted that, in the same way as NLR at time of metastasis, the prognostic markers described in the first group (NLM-group) lost their significance when lung metastasis were diagnosed. In this group of patients, gender was the only factor with a significant influence on survival. Therefore, we suggested that both NLR values (at the time of diagnosis and metastasis) should not be used as a prognostic factor for decision, making when lung involvement is diagnosed. However, nowadays, no prospective studies investigating the prognostic role of pretreatment NLR value in HNSCC with lung metastasis are reported. Few retrospective studies have explored the correlation between NLR and prognosis of HNSCC patients with disseminated disease [25]. For this purpose, Jin et al. conversely reported that pretreatment elevated NLR is significantly associated with a poor OS.

Nevertheless, regarding the LM-group, exploring the prognostic value of the NLR at time of metastasis should be done in a sensitive way. Concurrent and history of chemotherapy are well known to cause dynamical changes in the inflammatory markers that are monitored by the NLR prognostic tool. As a consequence, the need for establishing a NLR prognostic tool should be much more based on pretherapeutical measurements.

Additionally, prognostic factors for lung metastasis were demonstrated. First of all, our patients with a higher NLR at time of diagnosis developed more often lung metastasis. Furthermore, the multivariable analysis showed that increasing NLR was the only factor associated with poor LMFS. Kaplan–Meier analysis comparing LMFS between a high (> 2.62) or low (< 2.62) NLR values confirmed our findings. Consistent with our study, Yao et al. retrospectively evaluated the prognostic impact of hematological markers on distant-metastasis-free-survival (DMFS) in a cohort of 1550 patients with advanced naso-pharyngeal cancer. They confirmed that higher ratio NLR (> 2.5) and advanced N status (N2–N3) were associated with lower DMFS rate [26].

However, we should consider some limitations to our study. The main ones are the retrospective design with potential selection bias and confounding variables. The small number of patients and the heterogeneity in terms of treatment should be improved. Moreover, many of the hematological variables were assessed before diagnosis but there are no validated criteria for time of recording. For instance, patients simultaneously diagnosed with inflammatory condition (such as infection, abscess, …) had to be excluded. Further prospective studies are needed to confirm the results shown above and to refine the prognostic role of NLR. Nevertheless, it is to be noted that this study is a substantial one since the number of patients with lung metastasis is considerable.

Thus, pretreatment NLR value seems to be an interesting factor to assess the risk of disease progression and survival. Moreover, we highly suggest that hematological markers might offer useful tools in the treatment approach. An evidence based and validated hematologic model is needed, meanwhile, a case-by-case clinical approach is recommended.

Conclusion

In conclusion, our results support that pretreatment NLR ratio seems to be an independent prognosis marker of survival for HNSCC patients but not for HNSCC patients with lung metastasis. However, NLR has emerged as a useful tool for predicting lung metastasis dissemination. Physicians should, therefore, consider these results in identifying high-risk patients to improve decision making. These results need to be confirmed by prospective studies.

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Availability of data and materials The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The author(s) declare(s) that there is no conflict of interest.

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