Neutrophil-to-lymphocyte ratio as a predictor of survival in laryngeal carcinoma

Original Article

Authors

Joana Barreto
Hospital Pedro Hispano, ULS de Matosinhos, Portugal

Pedro Marques Gomes
Hospital Pedro Hispano, ULS de Matosinhos, Portugal

Delfim Duarte
Hospital Pedro Hispano, ULS de Matosinhos, Portugal

Miguel Viana
Hospital Pedro Hispano, ULS de Matosinhos, Portugal

Correspondence:
Joana Barreto
joanaccabarreto@gmail.com

Article received on July 16, 2024.
Accepted for publication on September 26, 2024.

Abstract

Introduction: The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory marker and is associated with a worse prognosis in various neoplasms. Recently, it has also been associated with a worse prognosis in laryngeal carcinoma.
Aim: To assess the association between NLR and survival in patients with laryngeal carcinoma at our institution.
Material and Methods: This retrospective study included 118 patients with laryngeal carcinoma treated at our institution. Pre-treatment NLR was assessed, as well as demographic characteristics and the American Joint Committee on Cancer (AJCC) prognostic stage. Patients with acute infections at the time of the analytical study were excluded. Cox regression was used for each of the variables alone to study their association with survival. The variables with a statistically significant result ($p<0.05$) were then included in a multivariate analysis to exclude potential confounding factors.
Results: A statistically significant association was found between NLR and survival, regardless of prognostic stage, with an adjusted Hazard Ratio of 1.22 ($p<0.001$).
Conclusion: NLR is an independent prognostic factor for survival in patients with laryngeal carcinoma. NLR can serve as a cost-effective prognostic biomarker.

Keywords: neutrophil-to-lymphocyte ratio; laryngeal carcinoma; survival.

Introduction

Laryngeal cancer is the second most common neoplasm of the upper aerodigestive tract after oral cavity carcinoma[1]. In Portugal alone, 529 new cases were detected in 2020, resulting in 329 deaths[1] . This disease predominantly affects men, with a global male-to-female ratio of 7:1[1].

The prognosis varies among patients, even for those with the same stage, as it depends on factors such as the immune status and

histological type[2]. Since each stage of the disease has specific characteristics, prognosis and risk of recurrence cannot be predicted by staging alone[3]. Inflammatory responses play a critical role in the onset and progression of various tumors[4]. The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory marker associated with poor prognosis in several neoplasms[3–5] and has recently been associated with worse outcomes in patients with laryngeal carcinoma[6,7].

Neutrophils, being inflammatory cells, may represent the inflammatory state of the tumor[2,8]. They produce vascular endothelial growth factors, which promote angiogenesis and tumor cell growth, thus facilitating invasion and metastasis[2,9,10]. Additionally, neutrophils secrete reactive oxygen species, nitric oxide, and arginase[9], which can suppress lymphocytes and natural killer cells[2]. In contrast, lymphocytes, a vital component of the immune system, suppress tumor cell proliferation and metastasis. Thus, a decreased lymphocyte count may indicate a poorer prognosis[2,10,11].

This study compared NLR values and survival rates of patients with laryngeal carcinoma treated at our center. While the literature reports different NLR cutoff points for predicting an increased mortality risk, the most recent meta-analysis on this topic suggested a cutoff value of 3[2].

Materials and methods

This retrospective study included 118 patients diagnosed with laryngeal carcinoma who were treated at our institution.

The NLR was calculated by dividing the number of neutrophils by the number of lymphocytes, which were evaluated before treatment. In addition, the demographic data of the patients and their prognostic stage, as defined by the American Joint Committee on Cancer (AJCC), were recorded. Laboratory tests were conducted one to two weeks prior to the surgery or initiation of medical treatment. Patients with acute infections at the time of the analysis were excluded from the study.

Cox regression analysis was performed for each variable individually to investigate its association with survival. Variables exhibiting statistically significant results ($p < 0.05$) were subsequently included in multivariate analysis to exclude potential confounding factors.

The Kaplan-Meier method was used to compare the survival rates of patients with an NLR <3 and NLR ≥3.

Results

The demographic characteristics and prognostic staging of the included patients are summarized in Table 1.

The median NLR in our sample was 2.57, with an interquartile range of 2.18.

Cox regression analysis of the association between survival rates and parameters of age, sex, smoking habits, alcohol consumption, tumor site, and histological type yielded no statistically significant results.

Conversely, both the prognostic stage defined by the AJCC and NLR demonstrated a statistically significant association with survival, which persisted in multivariate regression analysis (Table 2). Specifically, there was a statistically significant association between NLR and survival, regardless of the prognostic stage, with an adjusted hazard ratio of 1.22 ($p < 0.001$).

Kaplan-Meier curves comparing patients with an NLR <3 and NLR ≥3, stratified by stage, showed statistically significant results for more advanced stages (III and IV, with $p = 0.049$ and $p = 0.019$, respectively) in the log-rank test (Figure 1). However, no significant results were observed for the earlier stages.

Discussion

Both the prognostic stage defined by the AJCC and NLR demonstrated a statistically significant association with survival, which persisted in multivariate regression analysis. Specifically, there was a statistically significant association between NLR and survival, regardless of the prognostic stage, with an adjusted hazard ratio of 1.22 ($p < 0.001$). This indicates that for each 1-unit increase

Table 1
Demographic characteristics and prognostic staging

	(n=118)	
Age (years) - mean and SD	62,8 ± 9,4	
Sex - n (%)		
Male	115	(97,5)
Female	3	(2,5)
Observation time (years) - median and IQR	2,9	(5,4)
Smoking habit - n (%)		
Non-smoker	6	(5,6)
Ex-smoker	21	(19,6)
Smoker at diagnosis but quit	60	(56,1)
Smoker at diagnosis and maintained	20	(18,7)
Alcohol consumption - n (%)	58	(87,9)
Histological type - n (%)		
Squamous cell carcinoma	115	(97,5)
Sarcomatoid variant	2	(1,7)
Verrucous variant	1	(0,8)
T staging - n (%)		
Tis	2	(1,7)
T1	26	(22,0)
T2	23	(19,5)
T3	35	(29,7)
T4a	30	(25,4)
T4b	2	(1,7)
N staging - n (%)		
N0	77	(65,8)
N1	7	(6,0)
N2a	5	(4,3)
N2b	9	(7,7)
N2c	8	(6,8)
N3a	3	(2,5)
N3b	8	(6,8)
M staging - n (%)		
M0	111	(94,9)
M1	6	(5,1)
Prognostic stage - n (%)		
0	2	(1,7)
I	26	(22,2)
II	18	(15,4)
III	22	(18,8)
IVa	31	(26,5)
IVb	12	(10,3)
IVc	6	(5,1)
Site - n (%)		
Supraglottic	35	(29,7)
Glottic	82	(69,5)
Subglottic	1	(0,8)
Main treatment - (%)		
TLM	42	(35,6)
Total laryngectomy	50	(42,4)
CRT	14	(11,9)
RT	4	(3,4)
Palliative care	8	(6,8)
Postoperative adjuvant treatment - n (%)		
Not applicable	26	(22,0)
Surveillance	46	(39,0)
RT	29	(24,6)
CRT	17	(14,4)
Synchronous or metachronous neoplasms - n (%)	20	(16,9)
NLR - median and IQR	2,57	(2,2)

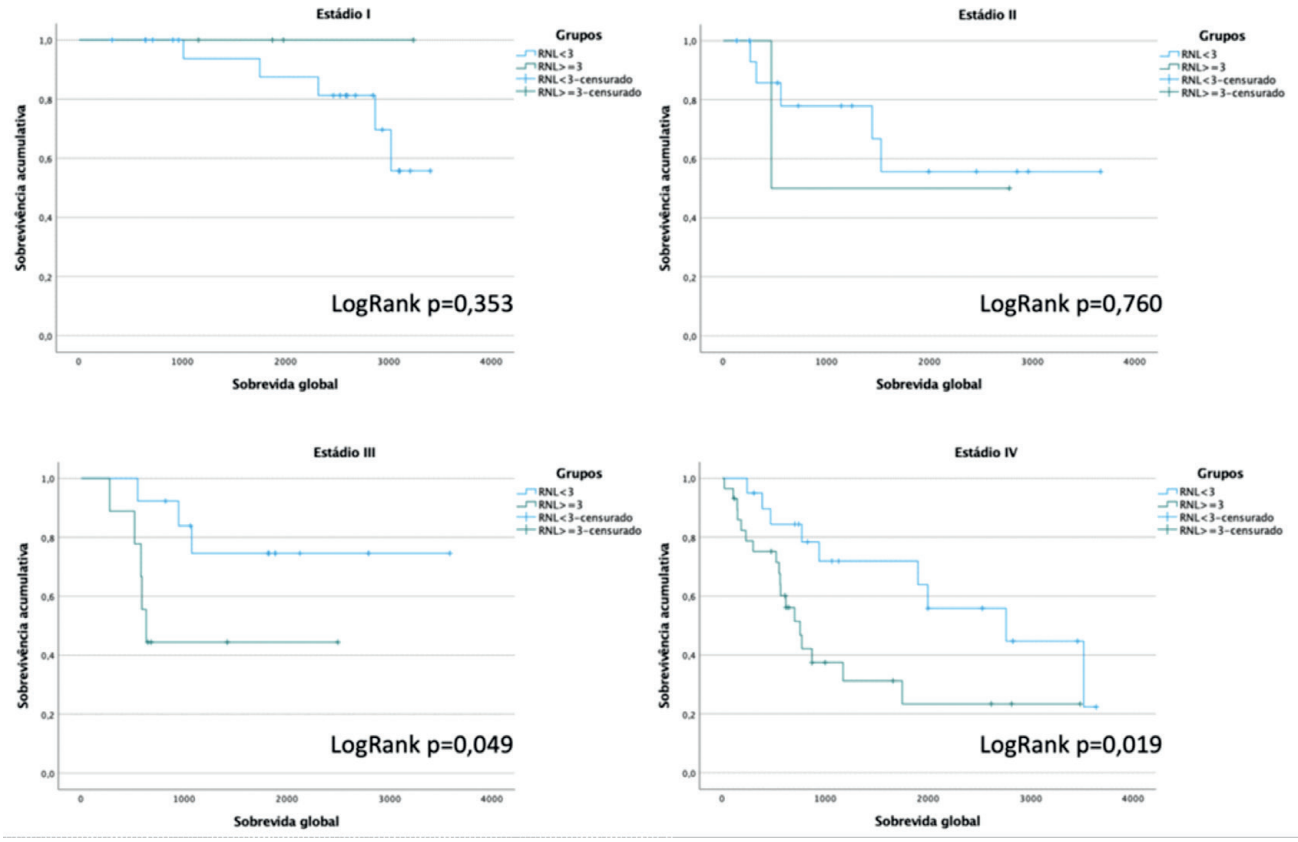
IQR - Interquartile Range; SD - Standard Deviation; TLM - Transoral Laser Microsurgery; CRT - Chemoradiotherapy; RT - Radiotherapy; NLR – Neutrophil-to-lymphocyte ratio. *11 missing values for smoking habits; 52 missing values for alcohol consumption; one missing value for N staging; one missing value for M staging; one missing value for prognostic stage.

Table 2
Hazard ratios (HR) in multivariate regression analysis

	Gross HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Prognostic stage						
I	0,035	0,009 - 0,127	<0,001	0,047	0,012 - 0,177	<0,001
II	0,097	0,029 - 0,321	<0,001	0,093	0,026 - 0,331	<0,001
III	0,08	0,025 - 0,257	<0,001	0,12	0,037 - 0,391	<0,001
IVA	0,14	0,049 - 0,402	<0,001	0,119	0,040 - 0,354	<0,001
IVB	0,279	0,087 - 0,895	0,032	0,28	0,085 - 0,921	0,036
IVC	1	1	1	1	1	1
NLR	1,209	1,141 - 1,282	<0,001	1,218	1,137 - 1,303	<0,001

ICI, confidence interval

Figure 1
Kaplan-Meier curves by the prognostic stage comparing the groups of patients with NLR < 3 and NLR≥3



in NLR, there is a 22% higher risk of death. Previous studies have reported different NLR cutoff values, ranging from 1.88–4.00[2], for prediction of increased risk of mortality in various neoplasms, including head and neck squamous cell carcinoma[2,4]. The most recent meta-analysis on this topic suggested a cutoff value of 3[2]. Kaplan-Meier curves comparing patients with an NLR <3 and NLR ≥3, stratified by stage, showed statistically significant results for more advanced stages (III and IV, with p = 0.049 and p = 0.019, respectively) according to the log-rank test. This suggests that a high NLR is a poor prognostic factor, especially in patients with more advanced stages. Although our study found no significant results for the earlier stages, this does not rule out the possibility of a relationship between NLR and survival at those stages.

In summary, NLR reflects the balance between the tumor's inflammatory response and the body's anti-tumor immune response. An elevated NLR indicates an inadequate immune response and development of a microenvironment favorable to tumor growth, which underscores its prognostic value, particularly in more advanced stages. As a simple and inexpensive marker, widely available through laboratory tests, NLR could potentially be used to identify patients at higher risk of mortality, such as those with an indication for adjuvant therapy.

Conclusion

The NLR is an independent prognostic factor for survival in patients with laryngeal carcinoma and may serve as a cost-effective prognostic biomarker. However, further studies are necessary to evaluate the clinical applicability of this biomarker in routine practice.

Conflict of Interests

The authors declare that they have no conflict of interest regarding this article.

Data Confidentiality

The authors declare that they followed the protocols of their work in publishing patient data.

Human and animal protection

The authors declare that the procedures followed are in accordance with the regulations established by the directors of the Commission for Clinical Research and Ethics and in accordance with the Declaration of Helsinki of the World Medical Association.

Privacy policy, informed consent and Ethics committee authorization

All the processed data were based in published reports that fulfilled privacy policy and ethical considerations.

Financial support

This work did not receive any grant contribution, funding or scholarship.

Scientific data availability

There are no publicly available datasets related to this work.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A. et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Cli. 2021 May;71(3):209-249. doi: 10.3322/caac.21660.
2. Hu X, Tian T, Sun Q, Jiang W. Prognostic value of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in laryngeal cancer: what should we expect from a meta-analysis? Front Oncol. 2022 Aug 10:12:945820. doi: 10.3389/fonc.2022.945820.
3. Zhao Y, Qin J, Qiu Z, Guo J, Chang W. Prognostic role of neutrophil-to-lymphocyte ratio to laryngeal squamous cell carcinoma: a meta-analysis. Braz J Otorhinolaryngol. 2022 Sep-Oct;88(5):717-724. doi: 10.1016/j.bjorl.2020.09.015.
4. Du J, Liu J, Zhang X, Chen X, Yu R, Gu D. et al. Pre-treatment neutrophil-to-lymphocyte ratio predicts survival in patients with laryngeal cancer. Oncol Lett. 2018 Feb;15(2):1664-1672. doi: 10.3892/ol.2017.7501.
5. Cai H, Zhang ZH, Zhou YJ, Liu J, Chen HQ, Lin RY. The prognostic value of preoperative plasma fibrinogen and neutrophil-to-lymphocyte ratio in patients with laryngeal squamous cell carcinoma. Ear Nose Throat J. 2021 Dec;100(10):731-736. doi: 10.1177/0145561320920746.
6. Chen L, Zeng H, Yang J, Lu Y, Zhang D, Wang J. et al. Survival and prognostic analysis of preoperative inflammatory markers in patients undergoing surgical resection for laryngeal squamous cell carcinoma. BMC Cancer. 2018 Aug 13;18(1):816. doi: 10.1186/s12885-018-4730-x.
7. Bojaxhiu B, Templeton AJ, Elicin O, Shelan M, Zaugg K, Walser M. et al. Relation of baseline neutrophil-to-lymphocyte ratio to survival and toxicity in head and neck cancer patients treated with (chemo-) radiation. Radiat Oncol. 2018 Nov 6;13(1):216. doi: 10.1186/s13014-018-1159-y.
8. Gooden MJ, de Bock GH, Leffers N, Daemen T, Nijman HW. The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. Br J Cancer. 2011 Jun 28;105(1):93-103. doi: 10.1038/bjc.2011.189.
9. Xun Y, Wang M, Sun H, Shi S, Guan B, Yu C. Prognostic analysis of preoperative inflammatory biomarkers in patients with laryngeal squamous cell carcinoma. Ear Nose Throat J. 2020 Jul;99(6):371-378. doi: 10.1177/0145561319876910.
10. Coffelt SB, Wellenstein MD, de Visser KE. Neutrophils in cancer: neutral no more. Nat Rev Cancer. 2016 Jul;16(7):431-46. doi: 10.1038/nrc.2016.52.
11. Wang J, Wang S, Song X, Zeng W, Wang S, Chen F. et al The prognostic value of systemic and local inflammation in patients with laryngeal squamous cell carcinoma. Onco Targets Ther. 2016 Nov 21:9:7177-7185. doi: 10.2147/OTT.S113307.