



Prognostic Nutritional Index as an independent prognostic factor in locoregionally advanced squamous cell head and neck cancer

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ABSTRACT

Background Locally advanced head and neck squamous cell carcinoma (LAHNSCC) is a heterogeneous disease in which better predictive and prognostic factors are needed. Apart from TNM stage, both systemic inflammation and poor nutritional status have a negative impact on survival.

Methods We retrospectively analysed two independent cohorts of a total of 145 patients with LAHNSCC treated with induction chemotherapy followed by concurrent chemoradiotherapy at two different academic institutions. Full clinical data, including the Prognostic Nutritional Index (PNI), neutrophil to lymphocyte ratio and derived neutrophil to lymphocyte ratio, were analysed in a training cohort of 50 patients. Receiver operating characteristic curve analysis was used to establish optimal cut-off. Univariate and multivariate analyses of prognostic factors for overall survival (OS) were performed. Independent predictors of OS identified in multivariate analysis were confirmed in a validation cohort of 95 patients.

Results In the univariate analysis, low PNI (PNI<45) ($p=0.001$), large primary tumour (T4) ($p=0.044$) and advanced lymph node disease (N2b-N3) ($p=0.025$) were significantly associated with poorer OS in the validation cohort. The independent prognostic factors in the multivariate analysis for OS identified in the training cohort were dRNL ($p=0.030$) and PNI ($p=0.042$). In the validation cohort, only the PNI remained as independent prognostic factor ($p=0.007$).

Conclusions PNI is a readily available, independent prognostic biomarker for OS in LAHNSCC. Adding PNI to tumour staging could improve individual risk stratification of patients with LAHNSCC in future clinical trials.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) includes a heterogeneous group of tumours that originate in different structures of this region, such as the oral cavity, oropharynx, hypopharynx and larynx. Inflammation plays an important role in the carcinogenesis of HNSCC, whether induced by the chronic action of chemical carcinogens, such as alcohol and tobacco,¹⁻⁴ or by the chronic

Key questions

What is already known about this subject?

- The main prognostic factors in head and neck squamous cell carcinoma are stage, site of disease and comorbidities.
- In the last decade, human papillomavirus has been identified as a common cause of and important prognostic factor in oropharyngeal cancer, conferring a better prognosis.
- In addition, systemic inflammation and nutritional status also play an important role in this disease. In many cancer types
- However, improvement in prognostic and predictive factors in head and neck squamous cell carcinoma is still a need not met at present.

What does this study add?

- The Prognostic Nutritional Index is an independent prognostic factor for locally advanced head and neck squamous cell carcinoma.

How might this impact on clinical practice?

- The Prognostic Nutritional Index may aid clinical decision making in locally advanced head and neck squamous cell carcinoma.
- The following are the main advantages stemming from the incorporation of the Prognostic Nutritional Index into the prognostic assessment of patients with locally advanced head and neck squamous cell cancer: (1) it is a surrogate marker of both systemic inflammation and nutritional status, and is robust, reproducible, inexpensive and universally available; and (2) it is a stage-independent trait, so it could be complementary to traditional prognostic factors without competing with them.

infection of oncogenic viruses, especially the human papillomavirus (HPV).⁵⁻⁸

Furthermore, evaluation of the nutritional status of patients with locally advanced head and neck squamous cell carcinoma (LAHNSCC) before treatment is considered mandatory for their proper management.⁹ In

fact, between 42% and 77% of patients with LAHNSCC present a high risk of malnutrition at diagnosis. In these patients, malnutrition has a multifactorial origin, due to problems with chewing and swallowing secondary to the disease itself, treatment-related toxicity, and malnutrition in relation to alcohol abuse.¹⁰ Therefore, a complete nutritional assessment is essential since it has been shown that nutritional impairment has a negative impact on clinical outcomes.^{11–13} It is worth noting that the presence of an inflammatory response may contribute to the development of cancer-associated malnutrition.¹⁴

The Prognostic Nutritional Index (PNI), calculated as previously described,¹⁵ may be especially useful due to its role as a surrogate marker of both inflammation and nutritional status. This index was originally studied to demonstrate the relation with postoperative complications and prognosis for patients affected by oesophageal carcinoma.¹⁶ A low PNI level has been subsequently correlated with a worse outcome in patients with hepatocellular carcinoma,^{17,18} lung cancer,¹⁹ bladder cancer²⁰ and other solid tumours. As regards HNSCC a low PNI has been shown to be a predictor of poor survival,²¹ and it has been associated with severe radiotherapy-induced adverse events in a small series of patients.²² In addition, there is increasing evidence supporting the role of neutrophils in tumour promotion, inflammation and immunosuppression associated with tumours.²³ On these bases, haematological biomarkers linked with inflammation, like the neutrophil to lymphocyte ratio (NLR)²⁴ and the derived neutrophil to lymphocyte ratio (dNLR),²⁵ have been developed and have shown their prognostic value in several solid tumours. However, data on the application of the aforementioned models in LAHNSCC are scarce.

The aim of the present study was to investigate in a training cohort and to confirm in an independent validation cohort the prognostic value of different haematological inflammation-based prognostic scoring systems such as the PNI and the NLR and their correlation with overall survival (OS) in patients with LAHNSCC.

PATIENTS AND METHODS

Study design

We conducted a retrospective review of the electronic patient records (EPR) of all patients with HNSCC treated by the Medical Oncology Department at two institutions—Hospital Universitari I Politècnic La Fe (HLF) and Hospital Clínico Universitario (HCU)—between May 2010 and May 2016 in order to produce a training set and a validation set of data, respectively.

All patients received the same scheme of induction chemotherapy (ICT) with cisplatin-5 fluorouracil and docetaxel. All patients received three-dimensional external radiotherapy. The concurrent chemotherapy regimen was either cisplatin 100 mg/m² every 21 days, cisplatin 40 mg/m² weekly or cetuximab 400 mg as loading dose with subsequent weekly 250 mg/m² following investigator criteria.

Patients and variables

All patients included should have had histologically confirmed LAHNSCC and have started ICT followed by concurrent chemoradiotherapy with radical intention. Baseline patient clinical factors collected included age, sex, date of diagnosis, Eastern Cooperative Oncology Group Performance status (*ECOG PS*), complete blood count (including absolute neutrophil and lymphocyte counts) and biochemistry (including albumin), HPV (human papillomavirus)/p16 status, and staging of the tumour (according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual Seventh Edition).²⁶

The NLR was calculated by dividing the baseline absolute peripheral neutrophil count (cells/mm³) by the absolute peripheral lymphocyte count (cells/mm³). The dNLR was defined as the quotient of the baseline absolute peripheral neutrophil count (cells/mm³) by the difference between the absolute baseline peripheral leucocyte count (cells/mm³) less the absolute baseline peripheral neutrophil count (cells/mm³).

The PNI was calculated as follows: $10 \times$ baseline serum albumin (g/dL) + $0.005 \times$ baseline absolute lymphocyte count (cells/mm³).

Patients with a history of inflammatory disease, an active concomitant infection, distant metastases at diagnosis, history of malignancy in the past 5 years or without baseline blood test results available were excluded.

Data collection

The EPR was reviewed for each patient, and all interesting data were retrieved in a joint database, properly encrypted and anonymised. Confidentiality of patients' data was kept throughout the study.

Statistical analysis

OS was calculated from the time of cancer diagnosis to death. Receiver operating characteristic (ROC) curve was used to determine the sensitivity and specificity similarities between the NLR, dNLR and PNI and to establish optimal thresholds for OS. The NLR, dNLR and PNI cut-off for OS prediction by ROC analysis were 2.6 (area under the curve, AUC=0.723), 1.7 (AUC=0.721) and 45 (AUC=0.695), respectively. These markers were analysed as categorical variables. Dichotomisation of these variables was based on the identified optimal cut-off as indicated above.

Continuous variables were presented as median and range and categorical variables were presented as frequencies. The presence of significant associations between clinical-pathological variables was determined using Mann-Whitney, Kruskal-Wallis, Student's t-test, χ^2 or Fisher's exact test as appropriate. Kaplan-Meier statistics and log-rank test were used to assess the impact of the different clinical factors associated with OS on univariate analysis. Univariate Cox regression was also performed with significant variables ($p < 0.05$), being further tested on a univariate multivariate stepwise backward Cox

regression model to validate their independent prognostic value in the training test cohort. Variables with a p value greater than 0.10 were removed from the model.

We used Harrel's concordance index (c-index) method to rank the different prognostic traits according to their predictive ability of discriminating patients according to OS. A c-index ($0.5 \leq \text{Harrel's c-index} \leq 1$) of 0.5 suggests no predictive discrimination power, while a c-index of 1.0 indicates perfect discriminatory power. c-Index was calculated as previously described by Uno *et al.*²⁷ The Akaike information criteria (AIC, lower is better) was used to assess relative goodness of fit. The ROC curve analysis was used to test the discriminative ability of the models. The model with the highest c-index and AUC and with the smallest AIC value was selected as the final model.

Independent prognostic factors identified by multivariate analysis in the training set (HLF) were further tested on the independent retrospective validation set from a separate cohort of patients (HCU) with similar clinical features.

For all analyses, the levels of statistical significance accepted were $p < 0.05$. Statistical analyses were performed using SPSS V.20.0 package and R Statistical Computing Environment (R Foundation, Vienna, Austria).

RESULTS

Patient characteristics

A total of 145 patients with LAHNSCC were included in this analysis. The training set consisted of 50 patients treated at HLF, whereas the validation set consisted of 95 patients treated at HCU.

The baseline characteristics of the training and validation sets were generally well comparable and are reported in [table 1](#). Most of the patients had ECOG PS=1. In both cohorts the majority of patients were men, around the fifth decade of life, with a history of tobacco use. Likewise, both in the training set and in the validation set, most of the patients presented with large primary tumours (T4) and advanced lymph node disease (N2b-N3), and were subsequently classified as stage IVA according to the TNM staging system of AJCC 2010 (seventh edition).²⁶ The main differences between the two cohorts are a higher proportion of unknown HPV in the training cohort (80% vs 52.7%) and a higher proportion of PNI-low (20% vs 32.6%) in the validation set.

On analysis, 22 and 34 patients in the training and validation sets, respectively, had died, with a median follow-up time of 21.5 months and 29.1 months, respectively. The median OS was 19 months in the training set, while it reached 62.9 months in the validation set. Kaplan-Meier plots of OS for both data sets are shown in ([figures 1 and 2](#)).

In the training set, the crude median PNI value was 42 (range: 28.1–62.1). Using ROC analysis, a value of 45 was selected as the optimal cut-off to dichotomise the PNI into two values, PNI-high versus PNI-low, reflecting an adequate versus impaired nutritional status, and

Table 1 Baseline characteristics of the 145 patients (training and validation sets)

Characteristics, n (%)	Training set (n=50)	Validation set (n=95)
Age (years), mean (range)	55 (41–59)	60 (43–77)
ECOG PS		
0	2 (4)	3 (3.2)
1	48 (96)	92 (96.8)
Sex		
Male	42 (84)	90 (94.7)
Female	8 (16)	5 (5.3)
Tobacco habit		
Yes	5 (10)	3 (8.6)
No	45 (90)	83 (91.6)
Unknown		5 (5.3)
Enolic habit		
Yes	18 (36)	13 (37.1)
No	12 (24)	22 (69.1)
Unknown	20 (40)	6 (6.3)
Primary tumour site		
Oral cavity	15 (30)	33 (34.8)
Oropharynx	12 (24)	15 (15.8)
Larynx	14 (28)	36 (37.9)
Hypopharynx	5 (10)	8 (8.4)
Other	4 (8)	3 (3.2)
T (TNM stage)		
T1-T3	20 (40)	5 (36.8)
T4	30 (60)	56 (58.9)
N (TNM stage)		
N0-N2a	22 (44)	39 (41.1)
N2b-N3	28 (56)	56 (58.9)
AJCC Cancer Staging System Seventh Edition		
Stage III	8 (16)	18 (18.9)
Stage IVA	41 (82)	61 (62.2)
Stage IVB	1 (2)	16 (16.8)
HPV/p16 status		
Positive	2 (4)	6 (6.3)
Negative	8 (16)	39 (41.1)
Unknown	40 (80)	50 (52.7)
NLR		
<2.6	23 (46)	50 (52.6)
≥2.6	27 (54)	45 (47.4)
dNLR		
<1.7	24 (48)	50 (52.6)
≥1.7	26 (52)	45 (47.4)
PNI		
PNI-high (>45)	40 (80)	57 (60)
PNI-low (<45)	10 (20)	31 (32.6)
Unknown	–	7 (7.4)

AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HPV, human papillomavirus; NLR, neutrophil to lymphocyte ratio; PNI, Prognostic Nutritional Index; dNLR, derived neutrophil to lymphocyte ratio.

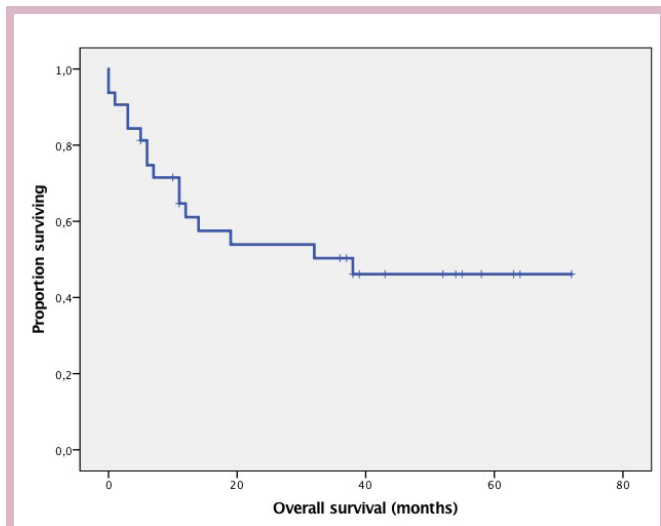


Figure 1 Kaplan-Meier overall survival (OS) curves in the training set (N=50).

consequently a low versus high risk of mortality (table 2). We also attempt to establish the optimal cut-off point for the analysis of a dichotomous NLR and a dichotomous dNLR and their link with OS by using ROC analysis. The highest sensitivity and specificity for predicting poor OS were met for $\text{NLR} \geq 2.6$ and $\text{dNLR} \geq 1.7$ and were therefore selected as the optimal thresholds for these inflammation-based prognostic scores (IBP) in this scenario (table 2). We compared the accuracy of the PNI and other IBP (dNLR and NLR) in predicting OS using ROC curve analysis, c-index and AIC. The comparison of models concluded that all potentially presented an adequate discrimination ability to predict OS and a good calibration, but PNI was the most balanced model, according to both AUC and c-index and AIC coefficients.

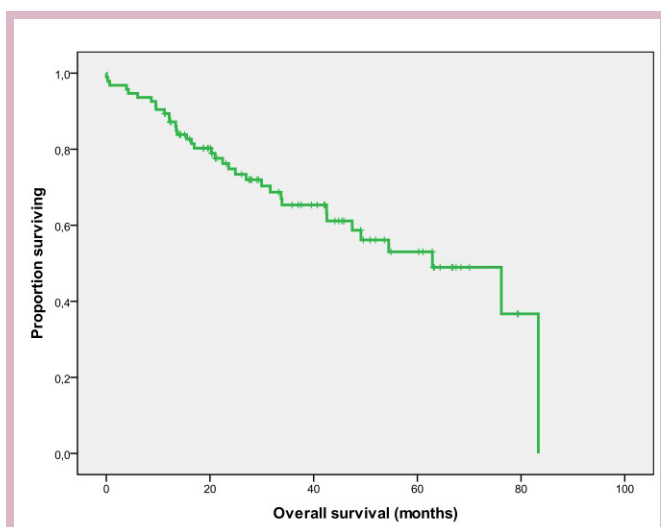


Figure 2 Kaplan-Meier overall survival (OS) curve in the validation set (N=95).

Qualification of the PNI as a predictor of OS in LAHNSCC

Univariate analysis of OS in the training set identified a low PNI score as a significant predictor of mortality with a 12-month OS of 72% for patients with PNI-low (<45) vs 90% for patients with PNI-high (≥ 45) ($p=0.042$). Other significant predictors of shorter OS on univariate analysis included a high NLR ($\text{NLR} \geq 2.6$) ($p=0.05$) and a high dNLR ($\text{dNLR} \geq 1.7$) ($p=0.02$). In contrast, some classic prognostic factors, such as tumour size (T4 vs T1-T3) ($p=0.262$), lymph node disease (N2b-3 vs N0-2a) ($p=0.792$) or ECOG PS ($p=0.345$) did not reach statistical significance (table 3).

Following multivariate analysis only PNI (HR 2.84, 95% CI 1.04 to 7.78, $p=0.042$) and dNLR (HR 3.53, 95% CI 1.13 to 11.03, $p=0.03$) retained independent prognostic power in the training patient cohort. However, NLR was not a significant predictor of OS on multivariate analysis in the training set (table 4).

Validation of the PNI as a predictor of OS in LAHNSCC

The prognostic ability of PNI was verified in an independent, retrospectively collected database of LAHNSCC. Patients with a low PNI score were more likely to have more advanced lymph node disease ($p=0.038$), more advanced TNM staging ($p=0.012$) and higher NLR and dNLR levels ($p=0.007$ and $p=0.44$, respectively). There was no significant association between PNI and primary tumour site ($p=0.465$), smoking ($p=0.705$), alcohol consumption ($p=0.524$), tumour size ($p=0.458$) and p16/HPV status ($p=0.634/p=0.534$).

In the univariate analysis, low PNI (PNI <45) ($p=0.001$), large primary tumour (T4) ($p=0.044$) and advanced lymph node disease (N2b-N3) ($p=0.025$) were significantly associated with poorer OS. In contrast, a high NLR and a high dNLR did not impact on OS (all p values >0.05) (table 3).

In the multivariate analysis, only PNI-low (HR 3.3, 95% CI 1.4 to 7.4, $p=0.0007$) and T4 (HR 3.2, 95% CI 1.08 to 9.54, $p=0.041$) maintained their significance as independent factors linked to an inferior OS. The HRs and 95% CIs for these independent factors are shown in table 4.

We compared the accuracy of the PNI and other IBP (dNLR and NLR) in predicting OS using ROC curve analysis, c-index and AIC. The comparison of models concluded that all potentially presented an adequate discrimination ability to predict OS and a good calibration, but PNI was the most balanced model, according to both AUC and c-index and AIC coefficients.

DISCUSSION

In this study, we identified and validated the prognostic value of PNI in patients with LAHNSCC treated with ICT followed by concurrent radiochemotherapy with curative intention. A low PNI was associated with a shorter survival, irrespective of other stage-related prognostic factors. Our study underlines the importance of baseline serum

Table 2 Comparison of optimal threshold, discrimination ability and internal calibration of haematological biomarkers inflammation-based

	NLR	dRNL	PNI
AUC ROC curve	0.72	0.73	0.70
Threshold established according to the ROC curve in the training set	2.6	1.7	45
Harrel's c index (c-index)	0.609	0.611	0.658
Akaike information criterion	142.61	125.93	121.88

AUC, area under the curve; NLR, neutrophil to lymphocyte ratio; PNI, Prognostic Nutritional Index; ROC, receiver operating characteristic; dRNL, derived neutrophil to lymphocyte ratio.

inflammatory indices for prediction of OS in LAHNSCC in this setting.

To date, the major advance in developing prognostic models in HNSCC has been the new classification for oropharyngeal carcinoma according to p16 status, which was adopted in the eighth edition of the AJCC TNM classification of malignant tumours, which was implemented in January 2018.²⁸ It has been paradigm-changing since it recognises p16-immunopositive oropharyngeal squamous cell carcinoma as a completely different biological and molecular entity. However, this subgroup represents only between 25% and 30% of our whole HNSCC population.

With regard to the factors included in our study, only NLR was already studied in HNSCC. A recent meta-analysis concluded that a high baseline NLR is associated with poor prognosis in patients with HNSCC.²⁹ Our initial observation on the univariate analysis was consistent with these results in the training set.

The potential advantage of this inflammation-based biomarker is that it may reflect the underlying immune status and host inflammatory response. Moreover, it

can be easily calculated for any patient, using routine pretreatment blood tests. It could be a promising prognostic biomarker since it has already shown correlation with OS in other cancer subtypes, including a small series of HNSCC in early stages. However, although all studied inflammatory markers were associated in our series with OS in the univariate analysis, PNI was the only one independently associated with OS in the multivariate analysis, in both training and validation cohorts. In contrast, there is still a lack of consensus on the optimal baseline NLR and dNLR threshold in this setting. Another weakness is that they can be very much influenced by external factors such as the use of corticosteroids or intercurrent infections.

On the other hand, PNI seems to be a more robust biomarker, with greater internal and external validity, and with less variability based on external factor. In addition, as other inflammation-based biomarker mentioned above, it is reproducible, inexpensive and universally available, with the advantage of providing reliable information about host nutritional status as well.

Table 3 Univariate analyses for overall survival in the training set (n=50) and in the validation set (n=95)

Variable	HR	95% CI	P values
Univariate analysis (Cox regression) in the training set (n=50)			
ECOG PS 1 vs 0	1.230	0.605 to 6.012	0.345
T4 vs T1-T3	1.9123	0.616 to 5.945	0.262
N2b-N3 vs N0-N2a	1.166	0.373 to 3.648	0.792
NLR ≥2.6 vs <2.6	2.829	0.90 to 8.80	0.73
dNLR ≥1.7 vs <1.7	3.539	1.129 to 11.038	0.03
PNI <45 vs ≥45	2.845	1.04 to 7.783	0.042
Univariate analysis (Cox regression) in the validation set (n=95)			
Variable	HR	95% CI	P values
ECOG PS 1 vs 0	1.148	0.629 to 5.980	0.280
T4 vs T1-T3	2.360	1.022 to 5.448	0.044
N2b-N3 vs N0-N2a	2.388	1.115 to 5.117	0.025
NLR ≥2.6 vs <2.6	1.232	0.633 to 2.40	0.539
dNLR ≥1.7 vs <1.7	1.487	0.762 to 2.902	0.245
PNI <45 vs ≥45	3.749	1.764 to 7.969	0.001

NLR, neutrophil to lymphocyte ratio; PNI, Prognostic Nutritional Index; PS, Eastern Cooperative Oncology Group Performance Status; dNLR, derived neutrophil to lymphocyte ratio.

Table 4 Multivariate analyses for overall survival in the training set (n=50) and in the validation set (n=95)

Variable	HR	95% CI	P values
Multivariate analysis (Cox regression) in the training set (n=50)			
NLR ≥ 2.6 vs < 2.6	2.829	0.91 to 8.80	0.073
dNLR ≥ 1.7 vs < 1.7	3.530	1.13 to 11.03	0.030
PNI < 45 vs ≥ 45	2.845	1.04 to 7.78	0.042
Multivariate analysis (Cox regression) in the validation set (n=95)			
T4 vs T1-T3	3.111	1.048 to 9.234	0.041
N2b-3 vs N0-N2a	2.191	0.861 to 5.578	0.90
PNI < 45 vs ≥ 45	3.019	1.347 to 6.768	0.007

NLR, neutrophil to lymphocyte ratio; PNI, Prognostic Nutritional Index; dNLR, derived neutrophil to lymphocyte ratio.

There are many advantages stemming from the incorporation of the PNI into the prognostic assessment of patients with LAHNSCC, some of which warrant further investigation in prospective studies. First, systemic inflammation represents a previously not comprehensively explored prognostic domain in this scenario. Second, since it is a stage-independent trait, it does not compete but rather ideally integrates with traditionally prognostic factors. Third, subjects displaying an ongoing inflammatory response may be at an additional risk of chemotherapy-related toxicity because of inflammation-related alterations in drug pharmacokinetics such as modulation of cytochrome P450 metabolism as well as hypoalbuminaemia³⁰; it could be helpful to clarify criteria for induction chemotherapy that remains controversial. Last, it could be interesting for future studies to determine if the dynamic changes in PNI after treatment may prove useful in evaluating therapeutic benefit in LAHNSCC.

One of the main strengths of this study is the external validation of our findings in an independent data set. However, it also has several limitations. First, it was a retrospective cohort study with exploratory intent. Moreover, given its retrospective nature and period of time of inclusion, tumours were staged according to the seventh edition of the AJCC TNM,²⁶ and p16 status, a well-established prognostic factor at present, was unknown in some patients. Furthermore, due to the retrospective nature of our study, we did not have accurate information available on treatment delays and dose reductions in the chemotherapy schedule. This was done according to standard of care in a routine clinical practice setting. We certainly admit they might slightly contribute to only small differences in survival between the training and validation sets. Nevertheless, since our ultimate goal was to describe a new independent prognostic factor, a more detailed analysis of these data exceeds the purpose of our study. Finally, prospective studies are needed to confirm the utility of PNI in risk stratification of LAHNSCC and potentially tailoring therapies.

In conclusion, we suggest the prognostic value of PNI in patients with LAHNSCC be composed of two routinely available and readily assessable factors: albumin and lymphocyte count. PNI could be useful in our daily

clinical practice to improve on prognostic assessment and to guide clinical decision making. Nevertheless, a prospective validation in a larger population is required.

Contributors All authors made substantial contribution to the conception and design of the study, and/or acquisition of data, and/or analysis and interpretation of data. All authors have participated in drafting the article. All authors gave final approval of the version to be submitted and to the revised version.

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Competing interests None declared.

Patient consent Not required.

Ethics approval This retrospective study was approved by the INCLIVA-Biomedical Research Institute Committee for Clinical Research and conducted in accordance with the principles of the Declaration of Helsinki.

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