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HEAD AND NECK

The prognostic-nutritional index in HPV-negative head and neck squamous cell carcinoma treated with upfront surgery: a multi-institutional series

Il prognostic-nutritional index nel carcinoma squamoso testa-collo HPV-negativo trattato chirurgicamente: studio multi-istituzionale

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SUMMARY

Objectives. To evaluate the prognostic value of pre-treatment prognostic-nutritional index (PNI) in patients with HPV-negative head and neck squamous cell carcinoma (HNSCC).

Methods. A multi-institutional retrospective series of HPV-negative, Stages II-IVB, HNSCCs treated with upfront surgery was evaluated. Correlation of pre-operative blood markers and PNI with 5-year overall (OS) and relapse-free (RFS) survival was tested using linear and restricted cubic spline models, as appropriate. The independent prognostic effect of patient-related features was assessed with multivariable models.

Results. The analysis was conducted on 542 patients. PNI ≥ 49.6 (HR = 0.52; 95% CI, 0.37-0.74) and Neutrophil-to-Lymphocyte Ratio (NLR) > 4.2 (HR = 1.58; 95% CI, 1.06-2.35) confirmed to be independent prognosticators of OS, whereas only PNI ≥ 49.6 (HR = 0.44; 95% CI, 0.29-0.66) was independently associated with RFS. Among pre-operative blood parameters, only higher values of albuninaemia and lymphocyte count (> 1.08 x 10^3/microL), and undetectable basophile count (= 0 10^3/microL) were independently associated with better OS and RFS.

Conclusions. PNI represents a reliable prognostic tool providing an independent measure of pre-operative immuno-metabolic performance. Its validity is supported by the independent prognostic role of albuminaemia and lymphocyte count, from which it is derived.

KEY WORDS: carcinoma, squamous cell of head and neck, lymphocytopenia, hypoalbuminaemia, basophils, index, prognostic nutritional

RIASSUNTO

***Obiettivi**. Valutare il valore prognostico dell'indice prognostico-nutrizionale (PNI) pre-trattamento nei pazienti con carcinoma a cellule squamose testa-collo (HNSCC) HPV-negativi.*

***Metodi**. È stata valutata una serie retrospettiva multi-istituzionale di HNSCC HPV-negativi, di stadio II-IVB, trattati con chirurgia upfront. La correlazione dei marcatori ematici pre-operatori e del PNI con la sopravvivenza globale (OS) e libera da recidiva (RFS) a 5 anni è stata testata utilizzando modelli linear and restricted cubic spline. L'effetto prognostico indipendente delle variabili correlate al paziente è stato valutato con modelli multivariabili.*

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Risultati. *L'analisi è stata condotta su 542 pazienti. PNI ≥ 49,6 (HR = 0,52; 95%CI, 0,37-0,74) e Neutrophile-to-Lymphocyte Ratio (NLR) > 4,2 (HR = 1,58; 95%CI, 1,06-2,35) si sono confermati fattori prognostici indipendenti di OS, mentre solo PNI ≥ 49,6 (HR = 0,44; 95% CI, 0,29-0,66) era associato in modo indipendente a RFS. Tra i parametri ematici pre-operatori, solo valori più elevati di albuminemia e conta dei linfociti (> 1,08 10^3/microL), e una conta dei basofili indosabile (= 0 10^3/microL) erano indipendentemente associati a una migliore OS e RFS.*
Conclusioni. *Il PNI rappresenta uno strumento prognostico affidabile che fornisce una misura indipendente della performance immuno-metabolica pre-operatoria. La sua validità è supportata dal ruolo prognostico indipendente dell'albuminemia e della conta linfocitaria, da cui deriva.*

PAROLE CHIAVE: *carcinoma squamocellulare testa-collo, linfocitopenia, ipoalbuminemia, basofili, indice prognostico nutrizionale*

Introduction

Although the negative prognostic role of malnutrition and consequent impairment of the immune-metabolic profile in cancer patients has been widely demonstrated [1], there is still a great disparity in the assessment and understanding of tumour- and patient-related characteristics in the pre-treatment setting. In fact, while the detailed analysis of clinical, radiological, and pathological features is nowadays considered mandatory, a thorough evaluation of the immune-metabolic performance status is still frequently neglected.

Head and neck squamous cell carcinoma (HNSCC) represents the 6th most common cancer worldwide [2], with 5-year overall survival (OS) ranging from 25% to 60% according to different subsites [3]. With the exception of the human papillomavirus (HPV) status which, however, only applies to oropharyngeal cancers, risk stratification in HNSCC is, so far, based exclusively on tumour-related parameters (e.g. site, stage, and grading) [4]. The integration of host-related risk factors into the currently available prognostic models may provide a more accurate and tailored risk stratification assessment with potential utility in both the prognostication of non-oropharyngeal cancers and in the heterogeneous subgroup of HPV-negative oropharyngeal cancers [5].

Screening of performance status in treatment-naïve patients should consider two crucial aspects, immune and metabolic, and can be accomplished through routine pre-treatment blood tests. Evaluation of immune performance, through quantitative analysis of peripheral leukocyte subpopulations, is based on the concept of cancer as a systemic disease, in which tumour-associated immune response and inflammation play a pivotal role in cancer development, progression, and distant spread [6,7]. Relative to metabolic performance, malnutrition is a common condition at cancer diagnosis with a complex multifactorial origin, resulting in cachexia, impairment of vital functions and reduced survival [1,8].

Based on the above evidence, in the attempt to further simplify and favour the inclusion of patient-related features in the therapeutic algorithm, many prognostic indices combining multiple blood parameters have been proposed. Among these, the "neutrophil-to-lymphocyte ratio" (NLR) [6] and the "prognostic-nutritional index" (PNI) [9] represent two of the most studied, validated and applied. However, despite the robust results obtained in head and neck cancer and other malignancies such as in non-small cell lung cancer [10], and the integration of data of both metabolic (albuminaemia) and immune (lymphocyte count) status, the application of PNI in HNSCC is still limited.

The aim of this study was therefore to evaluate the prognostic value of PNI and other blood indexes in HPV-negative HNSCC patients.

Materials and methods

Participants and data

A multicentric retrospective analysis of 1001 consecutive patients affected by primary HNSCC treated by upfront surgery (with or without adjuvant chemoradiotherapy [CRT]) from March 2004 to June 2018 was conducted at 8 Italian centres (Brescia, Ferrara, Padova, Pavia, Pordenone, Treviso, Trieste, and Verona) [11]. Inclusion criteria were: a) diagnosis of Stages II-IVB primary HNSCC originating from the oral cavity, oropharynx, larynx, and hypopharynx; b) upfront surgery performed as primary treatment with curative intent; c) availability of comprehensive pre-operative blood tests within two months prior to surgery. Exclusion criteria were: a) histologically proven p16+ and/or HPV-DNA-positive tumour; b) presence of distant metastasis at diagnosis; c) any previous treatment for HNSCC; d) clinical history of previous or synchronous cancer (at any site). Finally, 542 patients were eligible for the present analysis.

Medical records were retrieved to collect baseline demographics, clinical, tumour-, and treatment-related characteristics. Information regarding smoking habit and alcohol consumption were retrieved as well. Pre-operative routine blood tests included: red blood cell count (RBC, 10^3/microL); white blood cell count (WBC, 10^3/microL); platelet count (10^3/microL); haemoglobin (Hb, g/L); haematocrit (Hct, %); mean corpuscle volume (MCV, fL); neutrophil, lymphocyte, monocyte, basophil, and eosinophil counts (10^3/microL); and albumin (g/dL). For all patients, NLR and PNI were calculated as follows NLR = (Neutrophils [10^3/microL])/Lymphocytes [10^3/microL]) and PNI = 10 x Albumin (g/dL) + 0.005 x Lymphocytes/microL.

For all enrolled patients a follow-up with clinical-endoscopic examination every 1-3 months for the first year, every 3-4 months during the second year, and every 4-6 months after that was available. Chest CT-scan was done annually. Additional clinical or imaging diagnostic procedures were performed according to clinical presentation and local protocols.

Statistical analysis

Variables included in the analysis were expressed in terms of median, interquartile range (IQR), range of values and percentages. Differences in pre-operative parameters according to age, gender, site of tumour origin, pT and pN status, tumour grade and stage were tested with Wilcoxon-Mann-Whitney and Kruskall-Wallis tests, as appropriate.

Outcomes of interest were: OS, defined as the time from surgery to death from any cause; relapse-free survival (RFS), defined as the time from surgery to first relapse of disease (at any site). Linear assumption of continuous variables for each outcome was first assessed through plot inspection of Martingale residuals. Further investigation of the linear relationship between continuous variables and the outcome of interest was tested by modelling their effect with restricted cubic splines (RCS) and testing the non-linear component by Chunk tests and plots inspection. If a non-linear effect was shown, the variable was modelled with an RCS.

Blood parameters and indices derived (PNI and NLR) were plotted as continuous variables against 5-year probability of OS and RFS; in case of non-linear relationships, the plot was developed from an RCS model. Similarly, blood parameters, PNI and NLR were plotted against hazard ratio (HR) for each outcome of reference (OS and RFS), with median value set as reference (HR = 1), and relative 95% confidence interval (CI). In case of non-linear relationships, the plot was developed from an RCS model, as well.

Pre-operative blood-tests with non-linear effect, PNI, and NLR were categorised into two prognostic classes as determined by the cut-off found with the X-tile software, based on the Kaplan Meier method (3.6.1 - Yale University, New Haven, CT, USA) [12]. The minimum percent of the total patient cohort for each prognostic class was set at 10%. The patient dataset was randomly split into two halves. The software performed a log-rank test for survival analysis in the first half to set the ideal cut-off according to the lowest p value; once found, the second half was divided accordingly. Next, the same procedure was performed to find the ideal cut-off in the second and applied in the first half. Finally, the software performed a survival analysis of the entire dataset based on these optimal cut-offs. To overcome the problem of multiple cut-points selection (secondary to the random split of the dataset into two halves), the X-tile software performed the cross-validation according to the Monte-Carlo method: the above-described procedure was replicated 1000 times and the results were averaged (random population numbers set at 1000). When significant ($p < 0.05$), the single cut-offs were applied in the entire cohort to categorise patients into one of the two prognostic classes for each variable under investigation.

Univariate analysis using Cox proportional hazards model was performed for variables of main interest, and results expressed in terms of HR and 95% CI. Schoenfeld residuals were checked to assess the proportional hazard assumption. Survival curves with relative 95% CI and number of patients at risk by time were plotted using the Kaplan-Meier method and compared with the log-rank test [13].

The most relevant patient-, tumour- and treatment-related factors commonly considered in clinical practice and voluptuary habits that could influence blood parameters were employed to draft a multivariable analysis using Cox proportional-hazard model to assess how pre-operative blood markers affect survival outcomes. The role of NLR and PNI as independent prognosticators was assessed as well.

Statistical analysis was performed using R (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria); p values < 0.05 (two-tailed) were considered statistically significant.

Results

Demographics and clinical presentation

Five-hundred-forty-two patients were included [median (IQR) age, 67 (60-75) years; 392 (72.3%) men] (Tab. I). Patients were affected by SCC of the oral cavity, larynx, oropharynx and hypopharynx in 49.8%, 33.2%, 8.9% and 8.1% of cases, respectively. Association between pre-operative parameters according to age, gender, site of tumour origin, pT and pN status, tumour grade and stage are available in the Supplementary Material (Figs. S1-S13). A significant and progressive reduction in RBC and increase in WBC, particularly neutrophil count, was observed with higher tumour grade. Significantly higher WBC and neutrophil counts were found in patients with hypopharyngeal cancer. Patients affected by pT4 HNSCC showed lower albuminaemia and higher neutrophil counts.

Survival analysis

At the time of analysis, 219 patients (40.6%) were dead, and 172 (31.7%) experienced disease relapse (17.0%, 13.8%, and 13.7% local, regional and distant relapse, respectively). The median survival of patients alive at the end of the study was 66 months (Q1-Q3: 48-91). Five-year OS and RFS were 60.7% (95% CI, 56.5-65.2%) and 67.3% (95% CI, 63.2-71.5%), respectively.

Table I. Characteristics of the cohort of patients under study.

Variable	Median	IQR (Q1-Q3)
Age at diagnosis – yr	67	15 (60-75)
Time between pre-operative lab tests and surgery – days	20	18 (10-28)
Red blood cell (RBC) – 10^3/microL	4.54	0.73 (4.16-4.89)
White blood cell (WBC) – 10^3/microL	7.62	2.88 (6.35-9.23)
Platelets – 10^3/microL	227.5	93.7 (184.0-277.7)
Haemoglobin (Hb) – g/L	14.0	2 (13-15)
Haematocrit (Hct) – %	42.2	5.3 (39.5-44.8)
Mean corpuscle volume (MCV) – fL	93.2	8.2 (89.0-97.2)
Neutrophiles – 10^3/microL	4.84	2.57 (3.71-6.28)
Lymphocytes – 10^3/microL	1.80	0.81 (1.40-2.21)
Monocytes – 10^3/microL	0.60	0.31 (0.48-0.79)
Basophils – 10^3/microL	0.03	0.05 (0.01-0.06)
Eosinophils – 10^3/microL	0.15	0.15 (0.09-0.24)
Albumin – g/dL	4.01	0.49 (3.76-4.25)
Neutrophil to lymphocyte ratio (NLR)	2.59	1.72 (2.00-3.72)
Prognostic-nutritional index (PNI)	49.6	7.6 (45.9-53.5)
Variable	**N.**	**%**
Gender		
Male	392	72.3%
Female	150	27.7%
Smoking habit		
Never	119	23.9%
Former	111	22.3%
Current	267	53.7%
Missing	(45)	
Regular alcohol consumption (≥ 1 AU/day)		
Never	262	58.9%
Former	46	10.3%
Current	137	30.8%
Missing	(97)	
Site of origin		
Oral cavity	270	49.8%
Oropharynx	48	8.9%
Hypopharynx	44	8.1%
Larynx	180	33.2%
cT classification		
cT1	38	7.0%
cT2	177	32.7%
cT3	141	26.0%
cT4	186	34.3%
cN classification		
cN0	300	55.6%
cN1	78	14.4%
cN2a	17	3.1%
cN2b	97	18.0%
cN2c	47	8.7%

continues ▶

Table I. Characteristics of the cohort of patients under study (*follows*).

Variable	Median	IQR (Q1-Q3)
cN3	1	0.2%
Missing	(2)	
Clinical staging		
Stage I	16	3.0%
Stage II	130	24.0%
Stage III	121	22.3%
Stage IV	275	50.7%
Grading		
Low-grade	44	8.6%
Intermediate grade	309	60.2%
High-grade	160	31.2%
Missing	(29)	
pT classification		
pT1	18	3.3%
pT2	186	34.6%
pT3	142	26.4%
pT4	192	35.7%
Missing	(4)	
pN classification		
pN0	280	54.6%
pN1	56	10.9%
pN2a	14	2.7%
pN2b	57	11.1%
pN2c	28	5.5%
pN3a	2	0.4%
pN3b	76	14.8%
Missing	(29)	
Definitive staging		
Stage II	133	24.5%
Stage III	116	21.4%
Stage IVa	215	39.7%
Stage IVb	78	14.4%
Adjuvant (chemo)radiotherapy		
Not performed	239	44.7%
Performed	296	55.3%
Missing	(7)	

Correlation between pre-operative blood markers and OS

Among pre-operative blood markers, a linear relationship with a significant influence on OS was found for RBC (HR = 0.52, $p < 0.001$), MCV (HR = 1.02, $p = 0.006$), monocyte count (HR = 1.65, $p = 0.042$) and albumin (HR = 0.43, $p < 0.001$, Fig. 1). Although linear, the relationship of pre-operative WBC ($p = 0.288$) and neutrophil count ($p = 0.165$) values with OS was not significant.

The linear assumption was not observed for Hb, Hct, platelet, lymphocyte, eosinophil, and basophil counts. Hb ≤ 12.9 g/L (HR = 2.34, $p < 0.001$), Hct ≤ 38.8% (HR = 2.22, $p < 0.001$), platelet count ≤ 168 10^3/microL (HR = 1.74, $p < 0.001$), lymphocyte count ≤ 1.08 10^3/microL (HR = 2.13, $p < 0.001$, Fig. 1), basophil count > 0 10^3/microL (HR = 1.72, $p = 0.004$), and eosinophil count ≤ 0.07 (HR = 1.82, $p < 0.001$) were significant predictors of

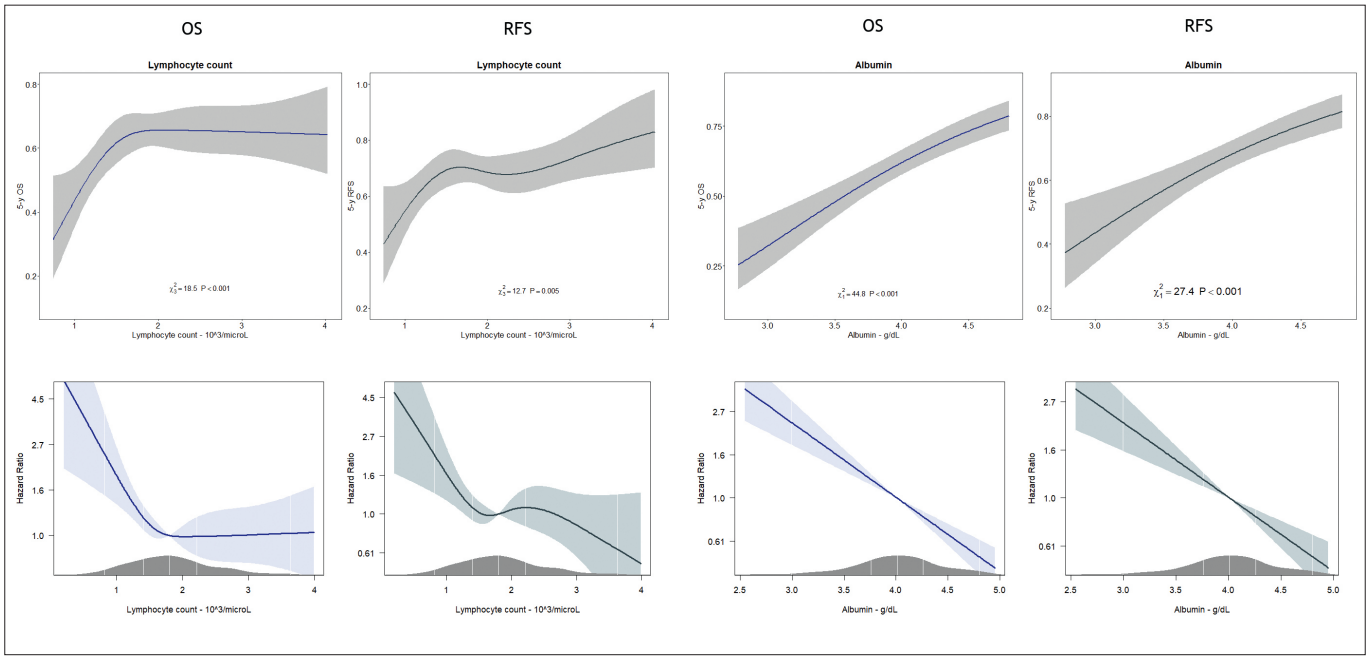

Figure 1. Non-linear and linear correlation of lymphocyte count and albuminaemia, respectively, in terms of both 5-year OS and RFS (first row). The corresponding HR plots are reported in the second row.

worse OS. Plots are reported in the Supplementary Material (Figs. S14-S17).

At multivariable analysis (Tab. II), once adjusted for patient-, tumour-, and treatment-related factors, among pre-operative blood markers, Hb ≤ 12.9 g/L (HR = 1.51, p = 0.041), lymphocyte count ≤ 1.08 10^3/microL (HR = 1.85, p = 0.014), basophil count > 0 10^3/microL (HR = 1.47, p = 0.014) and albuminaemia (HR = 0.57, p = 0.006 – continuous) maintained an independent prognostic influence on OS.

Correlation between pre-operative blood markers and RFS

A linear relationship with RFS was found for all pre-operative blood markers, except for lymphocyte and basophil counts. The linear correlation with RFS was significant for RBC (HR = 0.58, p < 0.001), Hb (HR = 0.84, p < 0.001), Hct (HR = 0.94, p = 0.001), MCV (HR = 1.02, p = 0.018), and albumin (HR = 0.46, p< 0.001, Fig.1), but not for platelet (p = 0.689), WBC (p = 0.228), neutrophil (p = 0.109), monocyte (p = 0.092) and eosinophil counts (p = 0.819). Lymphocyte count ≤ 1.08 × 10^3/microL (HR = 1.94, p = 0.002, Fig. 1) and basophil count > 0 10^3/microL (HR = 2.05, p = 0.001) were significantly associated with a higher risk of disease relapse. Plots are reported in the Supplementary Material (Figs. S18-S21). Lymphocyte count ≤ 1.08 × 10^3/microL (HR = 2.05, p = 0.011), basophil count > 0 × 10^3/microL (HR = 1.80, p = 0.035) and albuminaemia (HR = 0.51, p = 0.006 – continuous) maintained an independent prognostic influence on RFS once adjusted for the most relevant patient-, tumour- and treatment-related covariates (Tab. III).

Neutrophil-to-lymphocyte ratio and prognostic-nutritional index

Both NLR and PNI showed a linear effect, with a significant association at univariate analysis with all the outcomes under investigation (Tab. IV).

Once adjusted for patient-, tumour- and treatment-related factors, NLR was an independent prognostic factor for OS (HR = 1.10, p < 0.001), but not for RFS. PNI, however, confirmed its positive prognostic role as a continuous variable at multivariable analysis for both OS and RFS (Fig. 2).

For clinical application purposes, the optimal prognostic cut-offs for NLR and PNI were investigated to categorise each index into 2 prognostic classes. The ideal cut-off of NLR widely varied according to outcome under investigation. Once adjusted, the prognostic stratification based on NLR was independently associated only with OS (NLR > 4.2, HR = 1.58, p = 0.024).

The optimal cut-off for PNI was homogeneous according to the survival outcomes, and consistent with a PNI median value of 49.6. This prognostic stratification was significantly associated with any survival outcome at both uni- and multi-variable analysis. PNI ≥ 49.6 (HR = 0.52, p < 0.001) and PNI > 49.6 (HR = 0.44, p < 0.001) were independent predictors of better OS and RFS, respectively.

Table II. Univariate and multivariable analysis of pre-operative blood tests and the most relevant patient-, tumour- and treatment-related variables according to OS. Optimal cut-off for pre-operative blood tests was found with the X-tile analysis.

Overall survival (OS)		Univariate analysis		Multivariable analysis	
Variable	**Classes**	**HR (95% CI)**	**P-value**	**aHR (95% CI)**	**P-value**
Age at diagnosis – 10 yr increase	Linear	1.39 (1.24-1.57)	**< 0.001**	1.37 (1.17-1.60)	**< 0.001**
Gender	Female	Reference	0.736	Reference	0.853
	Male	1.05 (0.78-1.14)		0.96 (0.64-1.45)	
Smoking habit	Never smoker	Reference	0.597	Reference	0.330
	Smoker	1.09 (0.78-1.53)		1.35 (0.88-2.08)	
Regular alcohol consumption	Never	Reference	0.689	Reference	0.865
	Present or current	1.06 (0.79-1.43)		0.97 (0.69-1.37)	
Tumour origin	Hypopharynx	Reference		Reference	**0.088**
	Larynx	0.65 (0.40-1.04)	**0.074**		
	Oropharynx	0.59 (0.32-1.10)	**0.098**		
	Oral cavity	0.72 (0.46-1.14)	0.1650	1.41 (0.97-1.37)	
Tumour grade	G1-2	Reference	**< 0.001**	Reference	0.449
	G3	1.61 (1.21-2.13)		1.15 (0.80-1.66)	
pT classification	pT1-2	Reference		Reference	
	pT3	1.23 (0.85-1.76)	0.273	1.08 (0.67-1.75)	0.740
	pT4	2.11 (1.552.89)	**< 0.001**	1.76 (1.16-2.66)	**0.008**
pN classification	pN0	Reference		Reference	
	pN+ENE-	1.57 (1.10-2.23)	**0.012**	2.34 (1.48-3.69)	**< 0.001**
	pN+ENE+	3.63 (2.64-5.01)	**< 0.001**	4.87 (3.02-7.86)	**< 0.001**
Adjuvant RT	Not performed	Reference	**0.007**	Reference	**0.005**
	Performed	1.47 (1.11-1.93)		0.52 (0.33-0.82)	
RBC - 10^3/microL	Linear	0.52 (0.42-0.64)	**< 0.001**		
Haemoglobin (Hb) – g/L	> 12.9	Reference	**< 0.001**	Reference	**0.041**
	≤ 12.9	2.34 (1.77-3.10)		1.51 (1.02-2.23)	
Haematocrit (Hct) - %	> 38.8	Reference	**< 0.001**		
	≤ 38.8	2.22 (1.67-2.94)			
Mean corpuscle volume (MCV) – fL	Linear	1.02 (1.01-1.04)	**0.006**	1.02 (0.99-1.04)	0.120
Platelet count – 10^3/microL	> 168	Reference	**< 0.001**	Reference	0.216
	≤ 168	1.74 (1.27-2.40)		1.31 (0.85-2.01)	
WBC – 10^3/microL	Linear	1.03 (0.98-1.08)	0.288		
Neutrophil count – 10^3/microL	Linear	1.04 (0.98-1.10)	0.165	1.05 (0.97-1.14)	0.229
Lymphocyte count – 10^3/microL	> 1.08	Reference	**< 0.001**	Reference	**0.014**
	≤ 1.08	2.13 (1.47-3.09)		1.85 (1.13-3.01)	
Monocyte count – 10^3/microL	Linear	1.65 (1.02-2.69)	**0.042**	1.27 (0.68-2.35)	0.453
Basophil count – 10^3/microL	= 0	Reference	**0.004**	Reference	**0.014**
	> 0	1.72 (1.19-2.49)		1.47 (0.92-2.34)	
Eosinophil count – 10^3/microL	> 0.07	Reference	**< 0.001**	Reference	0.265
	≤ 0.07	1.82 (1.36-2.44)		1.25 (0.85-1.85)	
Albumin – g/dL	Linear	0.43 (0.33-0.55)	**< 0.001**	0.57 (0.38-0.85)	**0.006**

ENE, extranodal extension; G1, low-grade; G2, intermediate grade; G3, high grade; RBC, red blood cell count; RT, radiotherapy; WBC, white blood cell count; yr-years.

Discussion

Many prognostic indices have been formulated to predict survival outcomes in cancer patients. NLR and PNI are among the most studied and widely applied. The prognostic role of NLR in HNSCC has been extensively investigated and confirmed, as evident from the most recent inherent meta-analyses

Table III. Univariate and multivariable analysis of pre-operative blood tests and most relevant patient-, tumour- and treatment-related variables according to RFS. Optimal cut-off for pre-operative blood tests was found with the X-tile analysis.

Recurrence-free survival (RFS)		Univariate analysis		Multivariable analysis	
Variable	**Classes**	**HR (95% CI)**	**P-value**	**aHR (95% CI)**	**P-value**
Age at diagnosis – 10 yr increase	Linear	1.22 (1.07-1.39)	**0.003**	1.22 (1.02-1.44)	**0.025**
Gender	Female	Reference	0.715	Reference	0.128
	Male	0.94 (0.68-1.31)		0.70 (0.45-1.11)	
Smoking habit	Never smoker	Reference	0.989	Reference	0.961
	Smoker	1.00 (0.69-1.45)		1.01 (0.63-1.61)	
Regular alcohol consumption	Never	Reference	0.475		0.168
	Present or current	0.89 (0.62-1.24)		0.97 (0.64-1.48)	
Tumour origin	Hypopharynx	Reference		Reference	0.886
	Larynx	0.58 (0.34-0.99)	**0.048**		
	Oropharynx	0.65 (0.39-1.08)	0.434		
	Oral cavity	0.77 (0.41-1.47)	**0.097**	0.97 (0.64-1.48)	
Tumour grade	G1-2	Reference	**0.001**	Reference	0.470
	G3	1.68 (1.23-2.30)		1.16 (0.77-1.75)	
pT classification	pT1-2	Reference		Reference	
	pT3	1.27 (0.84-1.94)	0.257	1.30 (0.74-2.27)	0.357
	pT4	2.27 (1.59-3.25)	**< 0.001**	2.24 (1.39-3.63)	**< 0.001**
pN classification	pN0	Reference		Reference	
	pN+ENE-	2.11 (1.41-3.18)	**< 0.001**	2.82 (1.68-4.73)	**< 0.001**
	pN+ENE+	5.01 (3.46-7.26)	**< 0.001**	6.96 (4.09-11.85)	**< 0.001**
Adjuvant RT	Not performed	Reference	**< 0.001**	Reference	**0.024**
	Performed	1.98 (1.40-2.69)		0.55 (0.33-0.92)	
RBC – 10^3/microL	Linear	0.58 (0.45-0.74)	**< 0.001**		
Haemoglobin (Hb) – g/L	Linear	0.84 (0.77-0.93)	**< 0.001**	1.03 (0.89-1.19)	0.727
Haematocrit (Hct) – %	Linear	0.94 (0.92-0.98)	**0.001**		
Mean Corpuscle Volume (MCV) – fL	Linear	1.02 (1.00-1.04)	**0.018**	1.02 (0.99-1.04)	0.221
Platelet count – 10^3/microL (10 units increase)	Linear	1.00 (0.97-1.02)	0.689	1.00 (0.97-1.02)	0.857
WBC – 10^3/microL	Linear	1.03 (0.98-1.09)	0.228		
Neutrophil count – 10^3/microL	Linear	1.05 (0.99-1.12)	0.109	1.05 (0.96-1.16)	0.272
Lymphocyte count – 10^3/microL	>1.08	Reference	**0.002**	Reference	**0.011**
	≤1.08	1.94 (1.27-2.96)		2.05 (1.18-3.55)	
Monocyte count – 10^3/microL	Linear	1.60 (0.92-2.76)	**0.092**	1.37 (0.66-2.84)	0.403
Basophil count – 10^3/microL	= 0	Reference	**0.001**	Reference	**0.035**
	> 0	2.05 (1.32-3.18)		1.80 (1.04-3.12)	
Eosinophil count – 10^3/microL	Linear	1.11 (0.44-2.82)	0.819	1.26 (0.39-4.03)	0.698
Albumin – g/dL	Linear	0.46 (0.34-0.62)	**< 0.001**	0.51 (0.32-0.82)	**0.006**

ENE, extranodal extension; G1, low-grade; G2, intermediate grade; G3, high grade; RBC, red blood cell count; RT, radiotherapy, WBC, white blood cell count; yr-years.

published [6,14,15]. However, an inconsistent prognostic cut-off of the NLR value (1.92 to 5 for OS) emerges when analysing the results of the included studies, making the clinical applicability of this index sometimes unpractical.

The prognostic value of PNI in solid tumours has been extensively demonstrated, and the application of PNI in HNSCC encouraged [16] based on the solid evidence summarised by a recent meta-analysis [17] that confirmed the correlation between PNI and poor survival outcomes in HNSCC. Of the studies included in the meta-analysis, most were on nasopharyngeal cancer [18-24] or HNSCC treated with non-surgical protocols [25-27]. Four [28-31] reported the prognostic value of PNI in surgical patients, but only on specific subsites (oral cavity [28], hypopharynx [29,30], larynx [31]).

Table IV. Uni- and multi-variable analysis showing 5-year OS, RFS and the relative HR of NLR and PNI both as continuous and categorized variables.

Variable				Cox Proportional-Hazard model				Log-rank test
				HR (95% CI)	P-value	Adjusted HR (95% CI)*	P-value	5-year estimate overall survival
Neutrophil-Lymphocyte Ratio (NLR)	Continuous variable			1.10 (1.05-1.14)	**< 0.001**	1.10 (1.04-1.16)	**< 0.001**	
	Categorization according to X-tile analysis		P-value	Reference				
	Favourable prognosis	≤ 4.2	**0.002**			Reference		62.7% (58.1-67.7%)
	Poor prognosis	> 4.2		1.61 (1.17-2.21)	**0.003**	1.58 (1.06-2.35)	**0.024**	51.1% (41.7-62.7%)
Prognostic-Nutritional Index (PNI)	Continuous form			0.93 (0.91-0.95)	**< 0.001**	0.94 (0.91-0.97)	**< 0.001**	
	Categorization according to X-tile analysis		P-value					
	Poor prognosis	< 49.6	**< 0.001**	Reference		Reference		49.9% (44.0-56.7%)
	Favourable prognosis	≥ 49.6		0.44 (0.34-0.58)	**< 0.001**	0.52 (0.37-0.74)	**< 0.001**	71.3% (65.8-77.2%)
Relapse-free survival								
Neutrophil-Lymphocyte Ratio (NLR)	Continuous form			1.07 (1.02-1.12)	**0.003**	1.05 (0.98-1.12)	0.171	
	Categorization according to X-tile analysis		P-value					
	Favourable prognosis	≤ 3.3	**0.058**	Reference		Reference		70.5% (65.7-75.6%)
	Poor prognosis	> 3.3		1.47 (1.08-2.00)	**0.013**	1.19 (0.81-1.73)	0.381	60.8% (53.9-68.7%)
Prognostic Nutritional Index (PNI)	Continuous form			0.93 (0.91-0.96)	**< 0.001**	0.94 (0.91-0.97)	**< 0.001**	
	Categorization according to X-tile analysis		P-value					
	Poor prognosis	≤ 49.6	**0.016**	Reference		Reference		56.0% (50.1-62.6%)
	Favourable prognosis	> 49.6		0.43 (0.31-0.59)	**< 0.001**	0.44 (0.29-0.66)	**< 0.001**	78.3% (73.3-83.6%)

** Adjusted HRs to most relevant patient (age, gender, smoking habit, regular alcohol consumption), tumour (site of origin, grade of differentiation, pT, pN), and treatment-related (adjuvant RT) prognostic factors.*

For the first time, we herein investigated the prognostic role of PNI, NLR and other pre-operative immuno-metabolic parameters on a large series of patients affected by HPV-negative, Stages II-IV, HNSCC treated with curative intent by upfront surgery.

Prognostic-nutritional index

PNI showed the following advantages: 1) it was found to be independently associated with both OS and RFS, as a continuous linear variable and when categorised (with the same cut-off, corresponding to the median value, for both outcomes); 2) it is calculated from two independent prognostic parameters (lymphocyte count and albuminaemia) which convey crucial information from immune and metabolic performances, respectively.

The positive prognostic influence of albuminaemia in HNSCC patients undergoing surgery has been extensively studied and demonstrated [32]. Our results confirm the independent linear prognostic effect of albumin on any outcome, with a dramatic reduction in mortality and disease recurrence for each increase of 1 g/dl. Of note, lower albuminaemia was significantly associated with higher pT, pN and overall staging, likely due to altered oral intake in patients with advanced and more symptomatic HNSCC, although its prognostic role was independent of these covariates.

Although previously reported [33,34], in this study we further investigated the protective role of lymphocyte count, clearly depicting its non-linear correlation with OS and RFS, identifying an independent cut-off (1.08 10^3/microL), which was uniform for both outcomes and consistent with

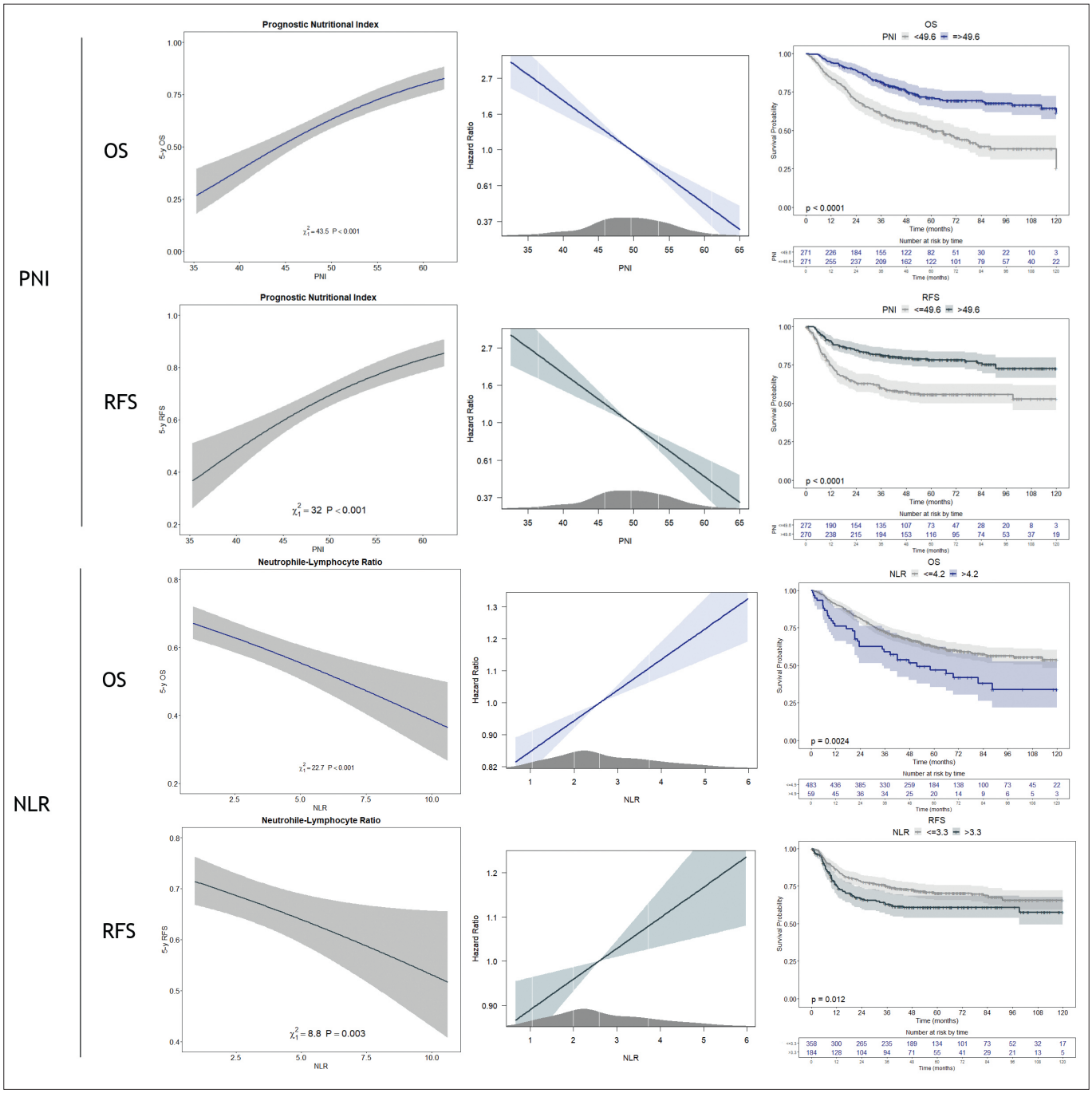

Figure 2. Linear models showing the correlation between pre-operative PNI and NLR and 5-year OS and RFS with relative HR plots. Kaplan-Meier survival curves (with relative 95% CI and table of patients at risk) show OS and RFS according to the prognostic classes found for PNI and NLR with the X-tile analysis.

the generally adopted definition of lymphocytopenia (< 1.0 10^3/microL). Below this threshold of "immunocompetence", a progressive increase in the risks of mortality and recurrence was reported, which was greater at lower lymphocyte counts. In contrast, no significant outcome changes were observed (especially for OS) for > 1.08 10^3/microL, suggesting a plateau in the protective effect of circulating lymphocytes. In addition, it is worth mentioning that lymphocyte count was not associated with tumour grade, pT, or pN stage, thus configuring as a host-related factor. These findings support the need for routine pre-operative screening for lymphocytopenia in patients with HNSCC, regardless of tumour characteristics. Furthermore, as recently demonstrated in other smoking-related cancers [35,36], PNI is

strongly correlated with tumour-infiltrating lymphocytes, a well-established prognostic marker even in HNSCC [7]. This result suggests that PNI, and hence circulating lymphocytes and albuminaemia, might reflect the host-tumour environment and the ability to effectively counteract tumour growth and spread.

Neutrophil-to-lymphocyte ratio

NLR has shown two major limitations: 1) its prognostic cut-offs varied widely for each outcome with a questionable reliability in the daily practice since it appears to be inconsistent not only among survival outcomes of interest, but also among studies, as seen in the published meta-analyses [14,15]; 2) it is calculated as the ratio of neutrophil to lymphocyte count, implying that increased neutrophil count and decreased lymphocyte count play a synergistic role in defining the increased risk of mortality and/or disease recurrence.

However, in contrast to previous reports [33,34], we did not find a significant association between neutrophil counts and any survival outcome. Furthermore, higher neutrophil count appeared to be related to hypopharyngeal, high-grade and high-stage tumours, which are well-known tumour-related risk factors. These findings suggest that higher values of pre-operative circulating neutrophils may be a consequence of advanced, aggressive, pro-inflammatory tumours.

Considering the strong prognostic role of lymphocyte count, the NLR as a prognostic tool for survival seems to depend solely on its denominator.

Other prognostic blood parameters

Higher Hb was an independent predictor of better OS, confirming previous experiences in HNSCC treatment [37,38]. Although a lower risk of disease recurrence was observed with increasing Hb, this correlation was not confirmed as independent.

Better OS was documented for platelet counts > 168 10^3/microL, although not confirmed as independent. This result is in contrast to what reported by a recent meta-analysis [39], in which increased mortality was demonstrated for higher platelet counts. It is worth mentioning that most studies categorised platelet count into two prognostic classes. In this regard, Rachidi et al. [40] stratified patients according to multiple cut-offs, showing the worst survival in patients with low (< 150) and high (> 315) platelet counts, although only the latter was an independent factor.

A negative linear effect of MCV on OS and RFS was found, although non-independent. The negative prognostic role of macrocytosis is confirmed by previous reports [41], and may be seen as an indicator of poor nutritional status associated with alcohol abuse, which is common in patients with HNSCC.

In addition, pre-operative basophil count > 0 10^3/microL was an independent negative prognostic factor in terms of both survival and recurrence risk. Few studies have investigated the prognostic role of basophil count in solid tumours, none in HNSCC, however always with mixed results [42,43]. Further studies on the biological mechanism underlying the role of basophils in cancer immune evasion are strongly warranted.

The immune-nutrition in modern head and neck cancer surgery

Over the past 2 decades, a new consciousness has developed around the importance of the immuno-metabolic characteristics of the cancer patient. Although the prognostic importance of intervening on metabolic deficits, such as hypoalbuminaemia, has long been known, the concept of immune-nutrition has only recently emerged. Immune-nutrition is defined as an intervention aimed at modulating the immune system and inflammatory response through the administration of specific nutrients [8]. Studies to date on the role of immuno-nutrition in patients undergoing surgery for HNSCC are generally small or of low quality, as shown by the recent meta-analysis by Howes et al. [44]. However, targeted nutritional interventions have been shown to decrease the risk of complications and length of stay, especially in the setting of salvage surgery after exclusive (C)RT, and to reduce the risk of toxicity with improved tolerance and quality of life in patients undergoing adjuvant treatments [8].

To understand which patients may benefit the most from interventions of immune-metabolic correction, many prognostic indexes have been developed. In this view, PNI represents a reliable prognostic tool that provides an independent measure of pre-operative immuno-metabolic performance in patients affected by HNSCC. Its validity is supported by the independent prognostic role of albuminaemia and lymphocyte count, from which it is derived.

Study strengths and limitations

The present study provides a prognostic analysis of the two most relevant and widely studied indexes in head and neck oncology, supported by a similar evaluation of each routinely available blood parameter in the pre-operative setting. In addition, the analyses were conducted on a large multicentre cohort of highly selected patients with strict inclusion criteria, followed regularly after treatment as recommended by the American Cancer Society.

On the other hand, the main limitation of the current study is its retrospective design. Also, given the long observation period, HNSCCs were staged according to the Seventh Edition of the American Joint Commission on Cancer TNM Staging System. However, due to the exclusion of HPV-positive HNSCCs, the differences between the Seventh and

Eighth Editions are quite limited. In addition, data on the waiting time between the onset of the first symptoms and treatment were not available, a variable that could have influenced the tumour stage and nutritional status of patients at the time of surgery. Finally, because we did not collect data on comorbidities, we could not determine the potential role of these variables on blood parameter values in our cohort of patients.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

MT, DB, PBR: study design and concept; MT, MCDM, GM, VG, PC, SP, PBR: data collection; MT, JP, PBR: data analysis; MT, CP, DB, PBR: writing and editing; CP, AD, PB, PN, PBR: critical revision.

Ethical consideration

In accordance with Italian regulations, the consent to participate was obtained from all alive patients while it was waived for those who were already dead. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Treviso and Belluno provinces (Date March 23th 2020/No. 773/CE Marca).

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