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Original Research Article

Neutrophil percentage-to-albumin ratio: is it useful in oropharyngeal cancer?

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ABSTRACT

Background: Host determinants, including nutritional status and systemic inflammation, are critical in the body's response to cancer. Neutrophil percentage-to-albumin ratio (NPAR) has emerged as a promising prognostic marker, however, its significance in head and neck cancer has yet to be fully established. This study aims to evaluate pretreatment NPAR as a predictor of disease-free survival, overall survival and cancer-specific survival in patients with oropharyngeal carcinoma.
Methods: This retrospective cohort study included 88 patients diagnosed with oropharyngeal squamous cell carcinoma (OPSCC) who underwent curative-intent treatment between January 1, 2010, and January 1, 2023. NPAR levels were assessed between diagnosis and treatment initiation. ROC analysis identified the optimal NPAR cutoff value of 16.09, which was used to categorize patients into low-NPAR and high-NPAR groups.
Results: High NPAR (≥16.09) was significantly associated with tumor persistence or recurrence (OR=5.70; p<0.001). Disease-free survival, 5-year overall survival and 5-year cancer-specific survival were all significantly shorter among patients with NPAR ≥16.09. In fact, high-level NPAR group had over than 3-fold increased risk of cancer-specific death at 5 years (HR=3.440; p=0.006).
Conclusions: Our findings indicate that a NPAR ≥16.09 may be associated with poorer outcomes in oropharyngeal cancer. While NPAR shows potential as a prognostic biomarker to complement the TNM staging system, further validation in larger, prospective studies is warranted.

Keywords: Oropharyngeal cancer, Biomarker, Disease-free survival, Recurrence, Survival analysis

INTRODUCTION

Oropharyngeal squamous cell carcinoma (OPSCC) comprises 11% of all head and neck squamous cell carcinomas (HNSCC), with its prevalence rapidly increasing, particularly in high-income countries.[1,2] Oropharyngeal cancer is primarily associated with three major extrinsic risk factors: tobacco use, alcohol consumption and oral HPV infection.[3] In fact, the 8th edition of the American joint committee on cancer staging manual differentiates between HPV-related and HPV-unrelated OPSCC, with the former subtype associated with better overall survival.[4,5]

However, the TNM staging system, which primarily focuses on tumor factors, overlooks host-related determinants, such as nutritional status and systemic inflammation-elements increasingly recognized as pivotal in cancer progression.[6] Inflammation is thought to facilitate tumor development by stimulating cell proliferation and angiogenesis.[7] Conversely, hypoalbuminemia, an indicator of chronic malnutrition, correlates with increased all-cause mortality.[8,9]

Recent research has focused on identifying potential inflammatory biomarkers to better predict treatment failure and survival outcomes in cancer patients.[10, 11]

NPAR has been proposed as a novel prognostic marker, correlating with poor outcomes in lung, bladder and pancreatic cancers.[12-14] However, to the best of our knowledge, its prognostic significance in head and neck cancer has only been evaluated in a single study involving patients with oral squamous cell carcinoma.[15]

Thus, we aim to assess the pretreatment NPAR as a predictor of disease-free survival (DFS), overall survival (OS) and cancer-specific survival (CSS) in patients with oropharyngeal carcinoma.

METHODS

Patient cohort

This retrospective study was conducted in the ENT department of a tertiary hospital in Portugal and was approved by the institutional review board and ethical committee (113/2024-1).

We included patients diagnosed with OPSCC from January 1, 2010, to January 1, 2023. All the selected patients received curative-intent treatment and underwent laboratory analyses (including hemogram and albumin measurements) before treatment initiation. Patients who received palliative/supportive care or died before treatment completion were excluded from the study.

Study variables

Demographic data included age, sex, body mass index (BMI), history of smoking and alcohol abuse and patient performance status at diagnosis-using Karnofsky performance status (KPS) scale and Eastern cooperative oncology group (ECOG) performance status scale.

We assessed the tumor's characteristics, including its location, p16 status and treatment modality. Tumor subsites were grouped into HPV-associated regions (palatine tonsils and base of tongue) and non-HPV-associated regions (oropharyngeal walls, soft palate and valleculae). Staging was determined according to the 8th edition of the American joint committee on cancer (AJCC) staging for head and neck cancer when p16 status was available.[4] In cases where p16 status was unknown, the 7th edition was used.

Pre-treatment laboratory data were collected and NPAR was calculated by dividing the neutrophil percentage of the total white blood cell count (%) by the albumin level (g/dL), using the same blood sample.

Outcomes

The primary outcome of interest was disease free survival (DFS), defined as the time between the end of treatment and the evidence of disease persistence or recurrence. Tumor persistence was defined as the presence of residual disease within 6 months following completion of treatment, while tumor recurrence referred to the reappearance of disease after a complete response, occurring more than 6 months post-treatment.

The secondary outcomes were 5-year cancer-specific survival and 5-year overall survival, measured from the date of diagnosis to cancer-related death or death from any cause, respectively.

Statistical analysis

Categorical variables were reported as frequencies and percentages, while continuous variables were summarized as means with standard deviations (SD) or medians with interquartile ranges (IQR), depending on distribution. Potential predictors of persistence/recurrence were analyzed using independent t test or Mann-Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables. ROC curve analysis was performed to determine the optimal cutoff value for NPAR in risk stratification. Survival analyses applied the Kaplan-Meier method, with log-rank test employed to compare survival distributions between groups. Statistical analyses were performed using SPSS version 25.0, with a significance threshold set at $p<0.05$.

RESULTS

Patient characteristics

The study population comprised 88 patients - 80 men (90.9%) and 8 women (9.1%)-with a mean age at diagnosis of 57.75 years (±SD 8.07) (Table 1). The median follow-up period was 2.63 years (IQR=3.42). Oropharyngeal cancers were most commonly located in HPV-associated regions, particularly the palatine tonsils (37.5%) and the base of tongue (18.2%). Among non-HPV-associated sites, the oropharyngeal walls were the most frequent location, accounting for 19.3% of cases.

p16 overexpression was detected in 11 patients, absent in 46 patients and unknown in 31 patients. Majority of patients (89.77%) were diagnosed with advanced-stage tumors (stage III/IV). Chemoradiotherapy as single treatment modality was performed in most patients (77.27%).

Clinicopathological factors predicting tumor persistence/recurrence

The cohort was divided into two groups based on the presence of tumor persistence or recurrence, and potential predictors were analyzed using bivariate analysis, as outlined in Table 1.

Body mass index at diagnosis was significantly lower in the persistence/recurrence group (21.20 kg/m^2) than in the persistence/recurrence-free group (23.0 kg/m^2), $p=0.029$. Persistence/recurrence rates were significantly higher in tumor stage IV (55.56%), compared to other

stages, p=0.011. Moreover, patients with history of alcohol abuse were nearly 3 times more likely to have tumor persistence/recurrence (OR=2.93, p=0.044).

Regarding pre-treatment laboratory parameters, the median NPAR was 15.39 across the entire cohort. A significantly higher NPAR was observed in the persistence/recurrence group (median NPAR=17.15) compared to the persistence/recurrence-free group (median NPAR=14.54), p=0.001.

Through ROC analysis, we identified a NPAR cut-off value of 16.09 for predicting disease persistence/ recurrence (AUC=0.709; p=0.001). In the total cohort, 34 patients (38.64%) had a NPAR≥16.09. We found an association between elevated NPAR (≥16.09) and tumor persistence/recurrence (OR=5.70; p<0.001).

Survival outcomes

Disease-free survival (DFS)

The overall prevalence of tumor persistence after treatment was 28.4% (n=25), with a recurrence rate of 17.0% (n=15). The median time from treatment completion to the detection of disease persistence/recurrence was 4 months (range: 0-130 months). Median disease-free survival, as estimated by Kaplan-Meier analysis, was significantly shorter among patients with NPAR ≥16.09 (Log rank test 16.016; p<0.001) (Figure 1).

The all-cause mortality rate was 54.5% (48 patients), with nearly half of these cases resulting from cancer-specific deaths (22 patients). The majority of the deaths (44 patients) occurred within the first 5 years of follow-up.

Five-year overall survival and cancer-specific survival

As illustrated in Figures 2 A and B, patients with NPAR ≥16.09 had significantly worse 5-year overall survival (Log rank test 15.504; p<0.001) and 5-year cancer-specific survival (Log Rank test 8.523; p=0.004). Univariate Cox regression analysis revealed that the high-level NPAR group had over than 3-fold increased risk of cancer-specific death at 5 years compared to the low-level NPAR group (HR=3.440; 95% CI=1.418-8.341; p=0.006).

Table 1: Baseline clinicopathological factors and tumor recurrence.

Variables	N (%)			P value
	Overall, (n=88)	No persistence/ recurrence group, (n=48)	Persistence/ recurrence group, (n=40)	
Age, mean (SD) (in years)	57.75 (8.07)	58.40 (6.73)	56.98 (9.46)	0.429
Sex				
Female	8 (9.10)	4 (50.0)	4 (50.0)	0.536
Male	80 (90.90)	44 (55.0)	36 (45.0)	
BMI, median (IQR), (kg/m^2)	22.40 (7.10)	23.0 (6.70)	21.20 (4.70)	0.029
Smoking status at diagnosis				
Current smoker	54 (62.10)	24 (44.44)	30 (55.56)	0.067
Former smoker	24 (27.60)	17 (70.83)	7 (29.17)	
Never smoker	9 (10.30)	6 (66.67)	3 (33.33)	
History of alcohol abuse				
Yes	63 (75.0)	29 (46.03)	34 (53.97)	0.044
No	21 (25.0)	15 (71.43)	6 (28.57)	
KPS score at diagnosis, median (IQR)	90 (10.0)	90 (10.0)	90 (10.0)	0.727
ECOG score at diagnosis				
0	22 (26.20)	14 (63.64)	8 (36.36)	0.356
1	58 (69.0)	32 (55.17)	26 (44.83)	
2	4 (4.80)	1 (25.0)	3 (75.0)	
Tumor subsite				
Palatine tonsil	33 (37.50)	18 (54.55)	15 (45.45)	0.901
Oropharyngeal walls	17 (19.30)	10 (58.82)	7 (41.18)	
Base of tongue	16 (18.20)	8 (50.0)	8 (50.0)	
Soft palate	13 (14.80)	6 (46.15)	7 (53.85)	
Valleculae	9 (10.20)	6 (66.67)	3 (33.33)	
p16 status				
Negative	46 (52.27)	28 (60.87)	18 (39.13)	0.079
Positive	11 (12.50)	10 (90.91)	1 (9.09)	
Unknown	31 (35.23)	10 (32.26)	21 (67.74)	

Continued.

Variables	N (%)			P value
	Overall, (n=88)	No persistence/ recurrence group, (n=48)	Persistence/ recurrence group, (n=40)	
Tumor clinical staging				
I	5 (5.70)	5 (100.0)	0 (0)	0.011
II	4 (4.55)	3 (75.0)	1 (25.0)	
III	16 (18.18)	12 (75.0)	4 (25.0)	
IV	63 (71.59)	28 (44.44)	35 (55.56)	
Treatment modality				
Chemoradiotherapy	68 (77.27)	38 (55.88)	30 (44.12)	0.562
Radiotherapy	9 (10.23)	3 (33.33)	6 (66.67)	
Surgery	2 (2.27)	1 (50.0)	1 (50.0)	
Neoadjuvant therapy + surgery	9 (10.23)	6 (66.67)	3 (33.33)	
NPAR, median (IQR)	15.39 (4.18)	14.54 (2.36)	17.15 (5.38)	0.001
Neutrophil percentage (%), mean (SD)	64.84 (8.74)	62.92 (8.17)	67.15 (8.93)	0.023
Albumin (g/dL), median (IQR)	4.20 (0.7)	4.35 (0.70)	4.0 (0.70)	0.001
NPAR group stratification				
Low-level (NPAR<16.09)	54 (61.36)	38 (70.37)	16 (29.63)	<0.001
High-level (NPAR≥16.09)	34 (38.64)	10 (29.41)	24 (70.59)	

BMI-Body mass index, KPS-Karnofsky performance status, ECOG-Eastern cooperative oncology group, NPAR- Neutrophil percentage-to-albumin ratio.

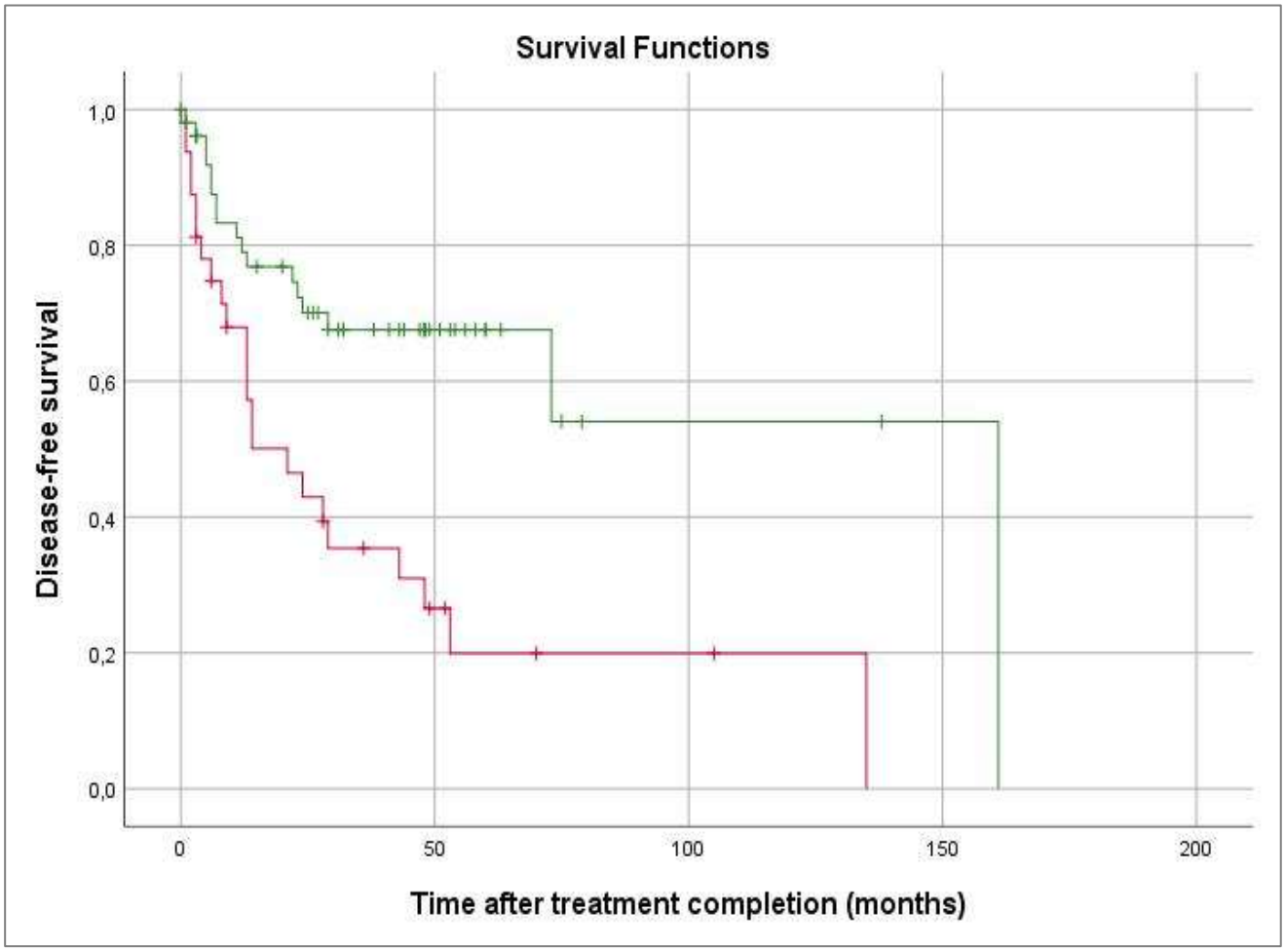

Figure 1: Disease-free survival time according to NPAR stratification.

*NPAR<16.09 (green line); NPAR≥16.09 (red line).

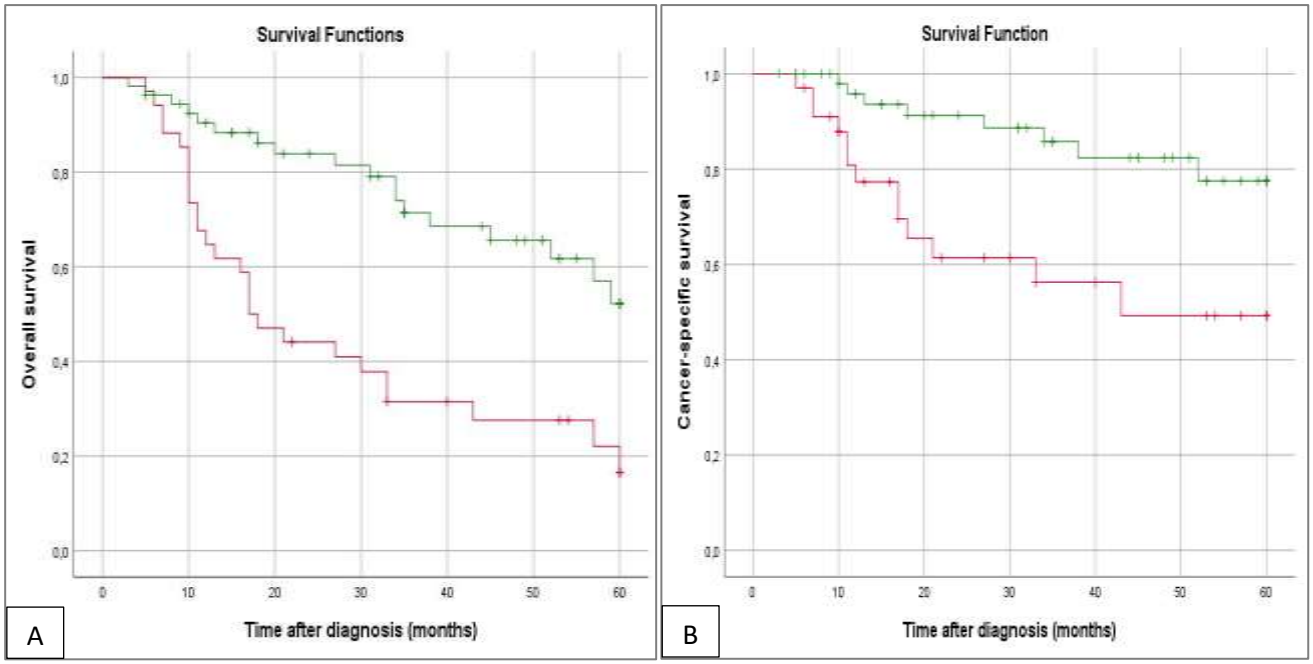

Figure 2: (A) 5-year overall survival according to NPAR stratification and (B) 5-year cancer-specific survival according to NPAR stratification

*A-NPAR<16.09 (green line); NPAR≥16.09 (red line). B-NPAR<16.09 (green line); NPAR≥16.09 (red line).

DISCUSSION

In recent decades, interest in the role of systemic inflammation and host immunity in oncogenesis has intensified. As cancer treatment options become increasingly diverse, there is an urgent need to develop a comprehensive set of prognostic indicators to enable more individualized patient management.[11,16]

Based on our current knowledge, this is the first study to assess the prognostic significance of pretreatment NPAR in patients with oropharyngeal cancer. Our findings indicate that patients with high NPAR (≥16.09) had an increased risk of disease persistence/recurrence. Furthermore, in our sample, a NPAR ≥16.09 was also associated with worse 5-year overall survival and 5-year cancer-specific survival.

We used the 16.09 threshold, determined through ROC curve analysis, to categorize patients into high and low NPAR groups. This cutoff aligns with the findings of Ko et al who studied patients with oral cavity squamous cell carcinoma undergoing curative surgery.[15] In their study, a high NPAR (≥16.93) was identified as an independent predictor of survival, associated with both poorer overall survival and reduced disease-free survival.

Our results are in line with emerging large-scale analyses that reported an association between elevated NPAR and increased mortality among cancer patients. In a population-based study, higher NPAR was independently linked to all-cause mortality and the cancer-related mortality.[17] Similarly, a multicenter cohort study validated neutrophil-to-albumin ratio as a robust prognostic marker for mortality across several malignancies.[18]

In a recent multicenter study, Ferro et al analyzed bladder cancer patients treated with neoadjuvant chemotherapy and radical cystectomy, concluding that those with a NPAR greater than 18 had significantly lower 5-year cancer-specific survival.[13] Varim et al demonstrated a correlation between high neutrophil-to-albumin ratio and advanced stages of non-small cell lung cancer.[12] Likewise, according to Tawfik et al neutrophil-to-albumin ratio was an independent predictor of pathological complete response in rectal cancer.[19]

Other researchers have demonstrated the negative impact of elevated NPAR on mortality, not only in cancer but also in various clinical settings, including heart failure, septic shock and chronic obstructive pulmonary disease.[20-22]

Research indicates that the composition of the tumor inflammatory microenvironment significantly influences cancer behavior.[7] However, the underlying mechanism linking NPAR to oncologic prognosis is still under investigation. Neutrophils, as key components of the tumor microenvironment, contribute to genetic instability, promote angiogenesis and tumor growth, and facilitate the invasive behavior of cancer cells.[23,24] Additionally, hypoalbuminemia reflects a state of increased catabolism, resulting from tumor-derived cytokines and tumor proliferation. Malnutrition and

comorbid conditions, such as chronic liver disease, further contribute to reduced serum albumin levels.[25,26]

Our findings suggest that NPAR may serve as a noteworthy prognostic biomarker in oropharyngeal cancer, providing clinical value due to its simplicity, reproducibility, and accessibility through routine blood tests. Consequently, active nutritional interventions and cancer immunotherapy strategies specifically targeting neutrophils could represent a promising approach for patients with elevated NPAR levels before treatment initiation.[27,28]

This study has several limitations that warrant consideration. First, its retrospective design, small sample size, single-center scope and the heterogeneity in treatment modalities may limit the generalizability of the findings. Another noteworthy limitation is the relatively short median follow-up of our cohort (2.63 years). Although 5-year overall survival and cancer-specific survival curves were estimated using the Kaplan-Meier method, the fact that a large proportion of patients did not reach the 5-year follow-up point may compromise the reliability of these long-term estimates. In addition, over 70% of patients in our cohort presented with stage IV disease, which may explain the high observed rate of tumor persistence/recurrence. This severity bias reduces variability within the cohort and limits the applicability of our findings to earlier-stage disease.

Ultimately, further prospective larger-scale studies, with extended follow-up are necessary to confirm the reliability of NPAR in the prognostic assessment of oropharyngeal cancer and to explore its potential impact on the TNM staging system.

CONCLUSION

Our findings indicate that a NPAR exceeding 16.09 may be associated with poorer prognosis in oropharyngeal cancer, including reduced disease-free survival, overall survival and cancer-specific survival. As an easily measurable parameter, NPAR holds promise as a prognostic biomarker for identifying patients at higher risk of treatment failure. However, these results require confirmation in larger, prospective studies before NPAR can be considered for integration into clinical practice.

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Ethical approval: The study was approved by the Institutional Ethics Committee (113/2024-1).

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