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Research

The Relationship Between Hemoglobin to Albumin Ratio and Disease-Free Survival in Patients with Locally Advanced Nasopharyngeal Cancer Treated with Chemoradiotherapy

Kemoradyoterapi ile Tedavi Edilen Lokal İleri Nazofaringeal Kanserli Hastalarda Hemoglobin-Albümin Oranı ile Hastalıksız Sağkalım Arasındaki İlişki

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ABSTRACT

Objective: The hemoglobin-to-albumin ratio (HAR) has been linked to survival in various cancers; however, its significance in nasopharyngeal carcinoma (NPC) remains unclear. This study aims to explore the relationship between HAR and disease-free survival (DFS) in NPC patients undergoing concurrent chemoradiotherapy (CRT).

Methods: This retrospective study included 30 patients with NPC who received concurrent CRT from January 2018 to December 2024. HAR was calculated as the ratio of hemoglobin to albumin. We performed Cox regression analyses to identify variables associated with DFS.

Results: Patients were classified into low- and high-HAR groups using the cut-off value determined by maximally selected rank statistics. DFS was 51.7 months in patients with low HAR and 29.8 months in patients with high HAR. We found a significant relationship between HAR and DFS (p=0.009).

Conclusion: A high HAR was associated with a poor prognosis in NPC patients treated with CRT.

Keywords: HAR, DFS, nasopharyngeal cancer, chemoradiotherapy

ÖZ

Amaç: Hemoglobin-albümin oranı (HAR) çeşitli kanserlerde sağkalımla ilişkilendirilmiştir, ancak nazofarengeal karsinomdaki (NPC) önemi hala belirsizdir. Bu çalışma, eşzamanlı kemoradyoterapi (CRT) uygulanan NPC hastalarında HAR ile hastalıksız sağkalım (DFS) arasındaki ilişkiyi araştırmayı amaçlamaktadır.

Gereç ve Yöntem: Bu retrospektif çalışmaya Ocak 2018 ile Aralık 2024 arasında eşzamanlı CRT alan NPC'li 30 hasta dahil edildi. HAR, hemoglobinin albümine oranı olarak hesaplandı. DFS ile ilişkili değişkenleri tanımlamak için Cox regresyon analizleri yapıldı.

Bulgular: Hastalar, maksimum seçilen sıralama istatistikleriyle belirlenen kesme değerine göre düşük ve yüksek HAR gruplarına ayrıldı. Düşük HAR hastalarında DFS 51,7 ay, yüksek HAR hastalarında 29,8 ay idi. HAR ve DFS arasında anlamlı bir ilişki bulduk (p=0,009).

Sonuç: Yüksek HAR, CRT ile tedavi edilen NPC hastaları için kötü prognoz ile ilişkiliydi.

Anahtar Kelimeler: HAR, DFS, nazofarenks kanseri, kemoradyoterapi

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a head and neck epithelial malignancy that shows a distinct geographic distribution, with the highest incidence in East and Southeast Asia (1). Advancements in diagnostic and therapeutic approaches, along with the widespread use of concurrent chemoradiotherapy (CRT), have significantly reduced the mortality rate of NPC (2).

Research indicates that cancer prognosis is linked not only to tumor characteristics but also to the patient's nutritional status and systemic inflammation (3).

Recently, various blood-derived markers have been used to create prognostic models for different malignancies, including NPC (4). These biomarkers include hemoglobin, albumin, the hemoglobin-to-albumin ratio (HAR), the neutrophil-lymphocyte ratio, the platelet-lymphocyte ratio, the monocyte-lymphocyte ratio, and the systemic immune-inflammation index (5). Hemoglobin and albumin are the two most common indicators of a patient's nutritional status (6). Research indicates that low preoperative serum albumin and hemoglobin levels are strongly associated with poor outcomes in patients with malignant tumors (7). Additionally, lower levels of hemoglobin and albumin were significantly associated with poorer overall survival in a cohort study of 8,093 patients with NPC (8). Furthermore, the HAR in gastric cancer patients has shown predictive value for short-term prognosis (9). However, the role of HAR in NPC is still not well understood. In this study, we aimed to clarify the prognostic significance of HAR in patients with NPC undergoing concurrent CRT. This study aimed to investigate the importance of HAR in assessing survival in NPC patients undergoing CRT.

METHODS

This retrospective study included a consecutive cohort of NPC patients who received concurrent CRT between January 2018 and December 2024. All patients underwent induction chemotherapy, followed by concurrent CRT. Primary inclusion criteria employed in this study were as follows: (I) previously untreated, locally advanced NPC confirmed by histological and radiological assessments, without evidence of metastasis; (II) definitive CRT combined with tri-weekly platinum-based concurrent chemotherapy; (III) age ≥18 years; (IV) availability of clinical, histological, and follow-up information; (V) no previous antitumor therapy. The primary exclusion criteria in this study were as follows: (I) a history of secondary cancer; (II) chronic inflammatory diseases; (III) an Eastern Cooperative Oncology Group-performance status (ECOG-PS) score of ≤70.

Clinicopathological information was extracted from the patient's medical records. Based on previous studies, variables related to NPC patients' prognosis were incorporated into the current study, including age, gender, T stage, and N stage. HAR was calculated as the ratio of hemoglobin to albumin.

Tumor response was assessed clinically by gynaecological physical examination and by conventional imaging 6 weeks after completion of treatment.

The final follow-up was conducted in December 2024. All patients were reviewed every three months for the first two years after treatment and every six months thereafter.

Disease-free survival (DFS) refers to the time from the date of NPC diagnosis to the date of disease recurrence or metastasis, or to the date of the last follow-up.

This study was approved by the Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no: 2025-03-01, date: 05.02.2025), was conducted in accordance with the precepts established by the Declaration of Helsinki, and informed consent was obtained from all the participants.

Statistical Analysis

The descriptive statistics of the data include mean, standard deviation, median, minimum, maximum, frequency, and ratio values. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the distribution of variables. The independent sample t-test was used to analyze quantitative independent data with a normal distribution. The Mann-Whitney U test was utilized to analyze independent quantitative data with a non-normal distribution. The chi-square test was employed to analyze independent qualitative data. Kaplan-Meier was used in the survival analysis. The SPSS 28.0 program was used in the analyses.

RESULTS

The patient characteristics are presented in the (Table 1). This retrospective study enrolled thirty patients with NPC. The mean age was 52.1±12.8 years. All patients had non-keratinizing squamous histology. Twenty-eight patients were male, and 23 had undifferentiated histology.

According to the tumor-node-metastasis (TNM) staging system, eight patients (26.7%) had stage II tumors, and 22 (73.3%) had stage III tumors. Twenty-six patients had an ECOG-PS of 0 and four had an ECOG-PS of 1.20% were positive for Epstein-Barr virus (EBV)-DNA and 6.7%

Table 1. Patient characteristics

Age (mean±standard deviation)	**52.1±12.8**
Gender (n, %)	
Male	28 (93.3)
Female	2 (6.7)
Histology (n, %)	
Differentiated	7 (23.3)
Undifferentiated	23 (76.7)
Stage (n, %)	
II	8 (26.7)
III	22 (73.3)
T stage (n, %)	
T2	12 (40.0)
T3	11 (36.7)
T4	7 (23.3)
N stage (n, %)	
N1	5 (16.7)
N2	24 (80.0)
N3	1 (3.3)
ECOG-PS (n, %)	
0	26 (86.7)
I	4 (13.3)
EBV-DNA (n, %)	
Positive	6 (20.0)
Negative	19 (63.3)
Unknown	5 (16.7)
HPV-DNA (n, %)	
Positive	2 (6.7)
Negative	9 (30.0)
Unknown	19 (63.3)
Type of induction agent (n, %)	
Cisplatin-gemcitabine	27 (90.0)
Carboplatin-gemcitabine	3 (10.0)
Treatment response (n, %)	
CR	18 (60.0)
PR	11 (36.7)
SD	1 (3.3)
Recurrence (n, %)	
Yes	21 (70.0)
No	9 (30.0)
Hemoglobin (mean)	14.3±1.9
Albumin (mean)	4.3±0.3
HAR (mean)	3.3±0.4

ECOG-PS: Eastern Cooperative Oncology Group-performance status, CR: Complete response, PR: Partial response, SD: Stable disease, HAR: Hemoglobin-to-albumin ratio, EBV: Epstein-Barr virus, HPV: Human papilloma virus

were positive for human papilloma virus (HPV)-DNA on pathological examination. All patients received induction chemotherapy (with cisplatin-gemcitabine or carboplatin-gemcitabine). Then, concurrent CRT, was administered with 29 patients showing an effective response complete response (CR)+partial response (PR) and one patient not responding as expected [stable disease (SD)], according to World Health Organization criteria. Recurrence (local, locoregional, or distant) occurred in nine patients (30.0%).

The mean hemoglobin and albumin values were 14.3±1.9 and 4.3±0.3, respectively. The mean HAR was 3.3±0.4. The median DFS was 43.1±7.4 months (Table 1).

In the univariate analysis, no significant differences were observed among age, gender, ECOG score, clinical stage, T stage, N stage, histological characteristics, and the presence of EBV or HPV with respect to DFS ($p>0.05$).

DFS was significantly lower ($p<0.05$) in the SD treatment response group (8.0 months) than in the CR (50.2 months) and PR (33.3 months) treatment response groups. DFS did not differ significantly between the treatment response groups with CR (50.2 months) and PR (33.3 months) ($p>0.05$) (Table 2).

No significant relationship existed between pretreatment hemoglobin and DFS, or between pretreatment albumin values and DFS ($p=0.228$ and $p=0.08$, respectively). DFS was 51.7 months in patients with low HAR and 29.8 months in patients with high HAR. We found a significant relationship between HAR and DFS ($p=0.009$; Figure 1).

Table 2. Univariate analysis for disease free survival

	Univariete model				
	HR	**95% CI**			**p-value**
Age	1.044	0.984	-	1.108	0.154
Gender	3.687	0.749	-	18.138	0.108
Histology	30.509	0.042	-	>100	0.310
Stage	1.212	0.251	-	5.848	0.811
T stage	1.039	0.434	-	2.483	0.932
N stage	0.985	0.256	-	3.784	0.983
ECOG-PS	1.596	0.189	-	13.464	0.668
EBV-DNA	0.778	0.250	-	2.425	0.666
HPV-DNA	1.545	0.365	-	6.541	0.555
Type of induction agent	0.475	0.050		4.052	0.449
Treatment response	6.203	1.539	-	25.002	**0.010**
Hemoglobin	0.835	0.622	-	1.120	0.228
Albumin	8.301	0.777	-	88.740	0.080
HAR	0.319	0.102	-	1.000	**0.009**

ECOG-PS: Eastern Cooperative Oncology Group-performance status, HAR: Hemoglobin-to-albumin ratio, EBV: Epstein-Barr virus, HPV: Human papilloma virus, HR. Hazard ratio, CI: Confidence interval

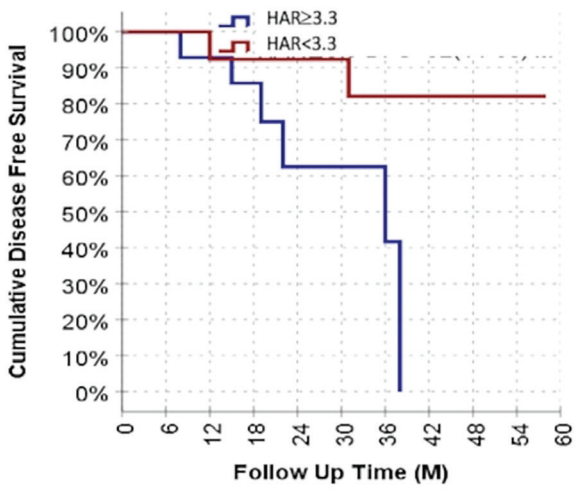

Figure 1. The relationship between HAR and DFS
HAR: Hemoglobin-to-albumin ratio, DFS: Disease-free survival

DISCUSSION

NPC is a relatively rare epithelial malignancy that exhibits significant regional variation. Historically, it has not received adequate attention or research (1). NPC exhibits considerable biological heterogeneity (10). According to the latest eighth edition of the TNM staging system, even among patients categorized in the same stage, survival outcomes can differ significantly when they undergo similar treatments (11). This indicates that the current anatomically based staging systems are insufficient for accurately predicting treatment effectiveness and patient prognosis. Our study showed no statistically significant differences in survival outcomes between stages.

Researchers are increasingly focusing on various clinicopathological factors and molecular biomarkers due to recent advancements in molecular biotechnology (12). EBV-DNA is a key marker with high sensitivity and specificity for the early diagnosis and screening of NPC (13). The predictive effectiveness of this method for staging and determining the prognosis of NPC is insufficient. In our trial, no statistically significant association was found between EBV-DNA and prognosis. These results may be due to the inability to evaluate the presence of EBV or HPV in all patients. Moreover, the fact that the study was conducted in a small, single center cohort may have influenced these results.

Genetic testing is costly, involves complex procedures, and has limited reproducibility. As a result, the widespread adoption of genetic testing for NPC still faces significant challenges. Ideal prognostic biomarkers are typically defined as characteristics that can independently identify an individual's prognosis. These biomarkers are designed to improve prognostic accuracy and provide multiple benefits. They are typically affordable, easily accessible and minimally invasive or non-invasive. Additionally, they provide clear indicators and can be scaled for implementation across various healthcare settings. Indicators identified through routine blood tests are associated with the most significant benefits (4).

The use of sub-parameters such as hemoglobin and albumin levels from routine tests—such as complete blood count and serum biochemistry—offers significant advantages over invasive histological examinations and costly genetic testing methods in clinical settings (4). Research suggests that hemoglobin levels affect oxygen transport, potentially leading to treatment-related complications and impacting the effectiveness of radiotherapy and chemotherapy (14).

Serum albumin is a crucial marker of nutritional status of cancer patients and an invaluable tool in their overall care and treatment (15). As cancer progresses, poor nutrition and inflammatory stress disrupt metabolism, leading to decreased albumin production and increased albumin consumption. This results in low serum albumin levels, a key predictor of prognosis in many types of cancer. Addressing these issues is vital for improving patient outcomes (4).

One trial revealed that TNM stage and HAR were significant independent prognostic factors for OS and PFS (16). We also found a significant relationship between HAR and DFS in our trial. High HAR was significantly associated with poor prognosis. However, there was no statistically significant association between the other clinical features and DFS.

Study Limitations

This study has some limitations. First, this was a single-center, small sample retrospective study. Second, several other inflammatory markers that correlate with prognosis were not included. Third, the hematological markers of NPC patients might fluctuate during treatment; for example, inflammation can reduce albumin levels, and chemotherapy can cause anemia, leading to variations in the HAR value at different time points. Therefore, multicenter, large-scale, prospective randomized controlled trials are necessary.

CONCLUSION

In this study, we showed that high HAR was associated with poor prognosis and was an independent predictor of outcome in NPC patients treated with CRT. Thus, the HAR score might be a convenient, non-invasive, affordable, and reliable tool to improve prognostication in NPC patients receiving CRT.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no: 2025-03-01, date: 05.02.2025), was conducted in accordance with the precepts established by the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all the participants.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: R.Ç., E.D., Concept: M.Y., Design: R.Ç., Data Collection or Processing: R.Ç., Analysis or Interpretation: C.K., S.Y.T., Literature Search: R.Ç., S.Y.T., M.Y., Writing: C.K., E.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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