RESEARCH ARTICLE / *Araştırma Makalesi*

Relationship between Hematological Inflammatory Markers and General Characteristics in Operable Cervical Cancer; State of the HALP Index

Ameliyat Edilebilir Rahim Ağzı Kanserinde Hematolojik İnflamatuar Belirteçler ile Genel Özellikler Arasındaki İlişki; HALP İndeksinin Yeri

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Geliş Tarihi / Received : **26.06.2023** Kabul Tarihi / Accepted: **16.08.2023** Çevrimiçi / Online: **30.09.2023**

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Cite this article/Atıf:
Bilir F, Batman D, Çorakçı A, Yücesoy İ. Relationship between Hematological Inflammatory Markers and General Characteristics in Operable Cervical Cancer; State of the HALP index. Sakarya Tıp Dergisi 2023;13(3): 384-389 DOI: 10.31832/smj.1319887

Abstract

Introduction	Cervical cancer is the most common gynecologic malignancy and the leading cause of cancer-related mortality in women worldwide. Systemic inflammatory reactions in cancer patients impact nutrition, function, and prognosis. Poor nutritional health is linked to a worse prognosis in several malignancies. A new score called the hemoglobin-albumin-lymphocyte-platelet (HALP) index was developed using dietary and inflammatory deficiencies.
Materials and Methods	This retrospective study and CC patients diagnosed from January 2012 to December 2020 who were operated for cervical cancer. Pre-treatment hemoglobin (Hb), albumin (Alb), lymphocyte count (Lc), and platelet (Plt) measurements were made for laboratory research.
Results	This retrospective study revealed 74 non-metastatic cervical cancer (median age was 55, ranging from 30 to 86 years). According to the FIGO stage, the percentage of stages 1 and 2 were 78% (58 patients), and 22% (16 patients). Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR), and HALP index were analyzed with LVSI, parametrial invasion, tumor size, histologic type, and duration of hospital stay; we could not find any significant correlation between the analysis.
Conclusion	NLR, PLR, and HALP index have no prognostic value in early operable cervical cancer patients regarding the pathologic features. Prospective multicenter and more patient studies will clarify how the hematologic parameters affect oncologic outcomes.
Keywords	HALP index, Cervical Cancer, Hematologic parameters, Prognostic value.

Öz

Amaç	*Rahim ağzı kanseri en yaygın jinekolojik malignitedir ve dünya çapında kadınlarda kansere bağlı ölümlerin önde gelen nedenidir. Kanser hastalarında sistemik inflamatuar reaksiyonlar beslenmeyi, fonksiyonları ve prognozu etkiler. Kötü beslenme sağlığı, birçok kanserde kötü prognozla bağlantılıdır. Hemoglobin-albümin-lenfosit-trombosit (HALP) indeksi adı verilen yeni bir skor, diyet ve enflamatuar belirteçleri kullanılarak geliştirilen bir indekstir.*
Yöntem ve Gereçler	*Bu retrospektif çalışma Ocak 2012-Aralık 2020 tarihleri arasında serviks kanseri nedeniyle opere edilen SK hastalarını retrospektif incelemiştir. Laboratuvar araştırması için tedavi öncesi hemoglobin (Hb), albümin (Alb), lenfosit sayısı (Lc) ve trombosit (Plt) ölçümleri yapıldı.*
Bulgular	*Bu retrospektif çalışma, 74 metastatik olmayan serviks kanserinden oluşmaktaydı (medyan yaş 55, 30 ila 86 arasındaydı). FIGO evresine göre evre 1 ve 2'nin yüzdesi %78 (58 hasta), %22 (16 hasta) idi. Nötrofil lenfosit oranı (NLR) ve trombosit lenfosit oranı (PLR) ve HALP indeksi, LVSI, parametriyal invazyon, tümör boyutu, histolojik tip ve hastanede kalış süresi ile analiz edildi; sonuç olarak analizler arasında anlamlı bir ilişki bulamadık.*
Sonuç	*NLR, PLR ve HALP indeksinin erken opere edilebilir serviks kanseri hastalarında patolojik özellikler açısından prognostik değeri yoktu. Prospektif çok merkezli ve daha fazla hasta sayısından oluşan çalışmalar, hematolojik parametrelerin onkolojik sonuçları nasıl etkilediğini netleştirecektir.*
Anahtar Kelimeler	*HALP indeksi, serviks kanseri, hematolojik belirteçler, prognostik değer*

INTRODUCTION

Cervical cancer (CC) is the most prevalent gynecologic malignancy and the main reason for cancer-related death in women globally. More than 600 000 new cases and approximately 342 000 deaths from CC were recorded in 2020, accounting for 7.7% of all female cancer-related mortality. Based on the disease stage, metastasis, or recurrence, several therapeutic techniques may improve the prognosis for CC. Patients with early-stage cervical squamous cell carcinoma typically undergo a radical hysterectomy and pelvic lymph node dissection for curative intent. Many recent research studies have examined the connection between inflammatory markers and cervical cancer. Several inflammatory markers have been linked to cervical cancer, and inflammation is a significant factor in the initiation and progression of cancer.

Recent studies have demonstrated that inflammatory markers associated to the tumor microenvironment have a significant prognostic value for various solid cancers. Systemic inflammatory reactions in cancer patients impact nutrition, function, and prognosis. Poor nutritional health is linked to a worse prognosis in several malignancies. The neutrophil-to-lymphocyte ratio (NLR) is a recognized indicator of patient survival for cancer. Also, It has been demonstrated that decreased survival in gynecological malignancies is associated with elevated NLRs prior to treatment. High NLR has been linked to the advanced stage, a short disease-free survival time, and poor overall survival (OS) in cervical cancer. The platelet-to-lymphocyte ratio (PLR) is a reliable marker of systemic inflammatory response. According to reports, PLR has an impact on the prognosis and effectiveness of treatment for a variety of malignancies, including ovarian cancer, gastric cancer, oesophageal cancer, and breast cancer. The likelihood of malignant tumor development and metastasis increases with higher PLR, which leads to a poor prognosis. Characteristics like age, tumor size, clinical stage, and lymph node metastases influence the prognosis of cervical cancer. Few studies focus on PLR as a predictor of cervical cancer, and they have conflicting results.

A new score called the hemoglobin-albumin-lymphocyte-platelet (HALP) index was developed using dietary and inflammatory deficiencies. In addition, utilizing this index may improve the accuracy of various cancer prognoses. There are only a few data about the HALP index and CC, but to our knowledge, there needs to be research about how this indicator had a prognostic value of CC in the Turkish Population.

MATERIALS and METHODS

Study Selection: After receiving approval from the Ethics Committee of the Faculty of Medicine, Kocaeli University (GOKAEK 2021-253), this retrospective study was carried out, which waived the requirement for written informed consent due to the study's retrospective nature. The confidentiality of patient data was guaranteed, as required by the Ethics Committee, and the Declaration of Helsinki conducted the study. CC patients diagnosed from January 2012 to December 2020 who operated for cervical cancer. FIGO stages 1a, 1b, and a selected stage 2 were the inclusion criteria. The study group includes histological categories of squamous cell carcinoma (SCC), adenocarcinoma (AD), or adenosquamous carcinoma (ASC). Receiving neoadjuvant therapy, two main malignancies, unintentional cancer (unexpected cervical cancer diagnosis following straightforward hysterectomy for a benign illness), pregnancy, any current infection, and insufficient HALP data were the exclusion criteria.

Data collection: Age, comorbidities (hypertension, diabetes, dyslipidemia), stage, histological type by World Health Organization (WHO) standards, tumor size, and treatment method were all gathered from the hospital database. Pre-treatment hemoglobin (Hb), albumin (Alb), lymphocyte count (Lc), and platelet (Plt) measurements were made for laboratory research.

The following equation was used to determine the HALP

index: Hb (g/L) x Alb (g/L) x Lymphocyte count (Lc)/ Platelet count (Pc) SPSS version 23.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. To find the best sensitive specific cutoff value to predict associated parameters, ROC curves of the parameters were created for the pretreatment NLR, PLR, and HALP index. The features of patients with and without relevant invasion and hematologic parameters were compared using the Pearson 2 test, the Fisher exact test, the independent T-test, and binary logistic regression analysis. The correlation between the variables was determined using Spearman's rho. The acceptable p-value cutoff for statistical significance was 0.05.

RESULTS

This retrospective study revealed 74 non-metastatic cervical cancer (median age was 55, ranging from 30 to 86 years). Other general characteristics are presented in Table 1. All patients were treated with modified radical hysterectomy or total abdominal hysterectomy, including bilateral salpingo-oophorectomy. According to the FIGO stage, the percentage of stages 1 and 2 were 78% (58 patients), and 22% (16 patients), as presented in Figure 1.

Table 1. General characteristics of the study population

Characteristics	Mean/Median Value	Standard Deviation/IR range	P value
Age, years	55	11/30-86	
Hemoglobulin gr/dl	12,4	1,2	
Platelet	283	84	
WBC, x10^6 cells/gr	8,200	3,0	
Neutrophil, x10^6 cells/gr	5,200	2,500	
Albumin g/dl	4	1.2	
NLR-pre	2,1	0,5-15	
NLR-post	5,7	1,2-30	<0.001
PLR-pre	126	20-300	
PLR-post	165	47-450	<0.001
HALP-pre	41	15-200	
HALP-post	19	7-120	<0.001

NLR: neutrophil-lymphocyte ratio, PLR: platelet lymphocyte ratio,

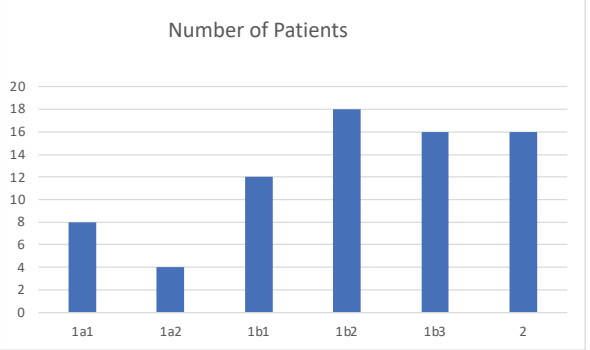

Figure 1: Patients distribution according to the stages.

Nineteen patients (25%) had adenocarcinoma, 26 patients (35%) had keratinized squamous cell carcinoma, 26 patients (35%) had non-keratinized squamous cell carcinoma, and the remaining three patients (4%) had other types (mixt type and neuroendocrine) diagnoses. Fifteen patients (20%) had parametrial invasion, 35 patients (47%) had a smaller than 2 cm tumor size, and 17 patients (23%) had a bigger than 4 cm tumor size. Twenty patients (27%) had a lymphovascular invasion.

Neutrophil lymphocyte ratio (NLR) significantly increased following the operation. Still, none of them showed a significant correlation between the pathologic parameters such as FIGO stage, parametrial invasion, T stage, and LVSI (p values were 0.3, 0.43, 0.9, and 0.26 preoperative and 0.19, 0.3, 0.07 and 0.9 postoperative term respectively). Similar to NLR, platelet lymphocyte ratio (PLR) could not show a significant correlation between the pathologic parameters (p values were 0.16, 0.24, 0.1, and 0.7 preoperative and 0.25, 0.4, 0.29 and 0.4 postoperative term respectively)

HALP index was analyzed with LVSI, parametrial invasion, tumor size, histologic type, and duration of hospital stay; we could not find any significant correlation between the analysis (presented in Table 2).

Table 2. Correlation Coefficient

Variable		1	2	3	4	5	6	7
1. Age, years								
2. Hospital Stay duration, days	Pearson Correlation	,370**						
	Sig. (2-tailed)	0,001						
3.Stage I and II	Pearson Correlation	,351**	,253*					
	Sig. (2-tailed)	0,002	0,030					
4.Parametrial invasion	Pearson Correlation	-,308**	-0,229	-,889**				
	Sig. (2-tailed)	0,008	0,050	0,000				
5.T stage, cm	Pearson Correlation	-0,067	-0,056	0,189	-,237*			
	Sig. (2-tailed)	0,568	0,633	0,107	0,042			
6. LVSI	Pearson Correlation	-0,035	0,040	-,364**	,450**	-,272*		
	Sig. (2-tailed)	0,769	0,735	0,001	0,000	0,019		
7. HALP pre	Pearson Correlation	0,083	0,073	0,147	-0,162	-0,133	-0,049	
	Sig. (2-tailed)	0,484	0,537	0,210	0,168	0,257	0,680	
8. HALP post	Pearson Correlation	0,022	-0,077	0,023	0,025	-0,182	0,087	,288*
	Sig. (2-tailed)	0,850	0,515	0,845	0,833	0,120	0,463	0,013

N:74, **. Correlation is significant at the 0.01 level (2-tailed)., *. Correlation is significant at the 0.05 level (2-tailed).LVSI: lympho-vascular space invasion,

Also, we analyzed FIGO stages 1a1, 1a2, 1b1, 1b2, 1b3, and stage 2 between the relation with NLR, PLR, and HALP index, but there were no significant relations with all parameters. In addition, we check all parameters before the operation and postoperation term. Both measurements did not show significant relations.

DISCUSSION

The present study found that patients diagnosed with early-stage cervical cancer had no significant relationship with hematologic inflammatory markers such as NLR, PLR, and HALP index, a new biomarker of nutrition and inflammation in the Turkish population.

Neutrophils can be mechanistically attracted to the tumor microenvironment, release proliferative factors, and inhibit T-lymphocyte activity, which promotes tumor progression, invasion, angiogenesis, and metastasis. The NLR is an independent predictive biomarker in several malignancies and is a systemic inflammatory indicative of the balance between antitumor immune response and protumor inflammation. While Zhang et al. demonstrated a link between preoperative NLR and unfavorable histological features and prognosis in cervical cancer patients who had surgery. Lima et al. revealed a negative association between NLR and prognosis in cervical cancer. In another study, Li et al. revealed that higher NLR was substantially linked with shorter OS and PFS, according to both univariate and multivariate survival analyses in stage IIB cervical cancer. Both studies have investigated late-stage cervical cancer compared to our research.

The platelet-to-lymphocyte ratio, or PLR, is a specific hematological measure that reflects the systemic inflammatory response. Reactive thrombocytosis, which occurs more frequently in solid tumors, is one aspect of the inflammatory response involving platelets. The host's systemic inflammatory response level is related to thrombocytosis and lymphopenia. A high PLR denotes either a relative drop in lymphocyte count or an increase in platelet count. Numerous studies have shown that PLR can be a poor prognostic factor for various malignant tumors and an indicator for assessing the immune function state. Gao et al. found that for the high PLR (PLR > 186.88) and low PLR

(PLR 186.88) groups, the 3-year OS values were 81.00% and 97.10%, respectively, while the 3-year PFS values were 59.50% and 88.20%, respectively in patients who treated with radiotherapy. Only 12% of patients in this study had FIGO stage 1 disease, and most were in an advanced stage. The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Index is a novel rating system that considers both nutritional condition and inflammation. It has been discovered that this index can increase the prognosis prediction accuracy for various malignancies. In a recent study, according to the survival curve, patients with low HALP scores (HALP score 39.50) in the two cohorts had significantly lower RFS rates and overall survival rates than patients with high HALP scores (HALP score 39.50) in operable cervical cancer patients. However, the HALP score alone had no substantial prognostic value for cervical cancer recurrence. To our knowledge th,s was the first extensive research HALP index and cervical cancer, and the authors concluded that a potential predictor for cervical cancer recurrence may be the HALP score. Cervical cancer recurrence can be more accurately predicted using a nomogram model based on the HALP score and traditional clinicopathological criteria.

Our study has significant limitations, such as comparing the hematologic parameters with pathologic features. We could not investigate the oncologic outcomes or survival rates. Also, this was single-center retrospective data, and we need to find more patients. Nonetheless, this preliminary research is the first investigation of the Turkish population's HALP index with cervical cancer.

In conclusion, NLR, PLR, and HALP index have no prognostic value in early operable cervical cancer patients regarding the pathologic features. Prospective multicenter and more patient studies will clarify how the hematologic parameters affect oncologic outcomes.

Kaynaklar

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