

## Research Article

# Relationship between Inflammatory Markers and General Characteristics in Endometrial Cancer; Prognostic Value of the HALP Index

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### Abstract

**Objectives:** A promising cancer-predictive biomarker is the hemoglobin, albumin, lymphocyte, and platelet (HALP) score, a comprehensive indicator of nutrition and systemic inflammation. There needs to be more data on the HALP index and EC, and to our knowledge, there is no investigation into how this indicator would have predicted EC in the Turkish population.

**Methods:** In this retrospective study, EC individuals with uterine cancer underwent surgery between January 2010 and December 2020, all data were collected from the hospital records.

**Results:** This retrospective study revealed 163 non-metastatic endometrial cancer (median age was 61, ranging from 41 to 84 years). The mean HALP index was 43 (min 10-max 115). HALP index levels were significantly decreased from FIGO stage I to stage III (mean values were 50, 40, and 27). Lymph node metastasis was detected in 11 patients with significantly lower HALP index compared to lymph node-free patients (30 vs 44,  $p=0.018$ ).

**Conclusion:** This is the first study in our population we found the HALP index is a good prognostic marker to predict pathologic features for early-stage endometrial cancer.

**Keywords:** HALP index, Endometrial Cancer, Hematologic parameters, Prognostic value

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Endometrial cancer is the sixth most prevalent cancer in women worldwide, with regional differences in incidence. The World Cancer Research Fund estimates that in 2020, roughly 400,000 new cancer cases and 2.6% of all cancer cases worldwide were diagnosed. Over time, the prevalence has consistently increased, mainly explained by changing lifestyles, hormonal variables, and an aging population.<sup>[1]</sup> Two to five percent of cases begin before the age of 40, while the frequency increases between the ages of 60 and 70. Endometrial cancer in patients under 50 is fre-

quently linked to chronic anovulation and obesity. About 80% of endometrial carcinomas are type I tumors, which include endometrioid tumors with grade 1 or 2 histology. An intraepithelial neoplasm may precede these tumors, are estrogen-induced and sensitive to progestins, and usually have a favorable prognosis. 10 to 20 percent of endometrial carcinomas are type II tumors. They comprise grade 3 endometrioid tumors in addition to serous, clear cell, mucinous, squamous, transitional cell, mesonephric, and undifferentiated tumors with non-endometrioid histology.<sup>[2,3]</sup>

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Recent studies have demonstrated the strong predictive usefulness of tumor microenvironment-related inflammatory markers for various solid malignancies. Systemic inflammatory reactions in cancer patients impact nutrition, function, and prognosis. A worse prognosis is associated with numerous cancers and poor nutritional health.<sup>[4]</sup> A promising cancer-predictive biomarker is the hemoglobin, albumin, lymphocyte, and platelet (HALP) score, a comprehensive indicator of nutrition and systemic inflammation.<sup>[5]</sup> HALP may also indicate cancer-related anemia, which is most likely a result of advanced disease, nutritional deficiencies, and ongoing blood loss.<sup>[6]</sup>

There needs to be more data on the HALP index and EC, and to our knowledge, there is no investigation into how this indicator would have predicted EC in the Turkish population.

## Methods

### Study Selection

This retrospective study and the Ethics Committee's regulations and the Declaration of Helsinki were followed when conducting the study, which required the confidentiality of patient data to be guaranteed. EC individuals with uterine cancer underwent surgery between January 2010 and December 2020. Histological carcinoma of the endometrioid type was included in the study group. Among the exclusion criteria were receiving neoadjuvant therapy, cancers other than endometrioid type EC, pregnancy, active infections, and insufficient HALP data.

### Data Collection

From the hospital database, the following information was taken: age, comorbidities (hypertension, diabetes, dyslipidemia), stage, histological type according to WHO standards, tumor size, and manner of therapy. For laboratory study, measurements of pre-treatment hemoglobin (Hb), albumin (Alb), lymphocyte count (Lc), and platelet (Plt) levels were taken. The following equation was used to determine the HALP index:  $Hb (g/L) \times Alb (g/L) \times Lymphocyte\ count (Lc)/Platelet\ count (Pc)$

SPSS version 23.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. For the pretreatment NLR, PLR, and HALP index, ROC curves of the parameters were generated to discover the most sensitive specific cutoff value to predict associated parameters. The characteristics of patients with and without pertinent invasion and hematologic parameters were compared using the Pearson 2 test, the Fisher exact test, the independent T-test, and binary logistic regression analysis. Using Spearman's rho, the correlation between the variables was calculated. The accepted 0.05 p-value criterion was used to determine statistical significance.

## Results

This retrospective study revealed 163 non-metastatic endometrial cancer (median age was 61, ranging from 41 to 84 years). According to the FIGO staging, 42% of stage I, 46% of stage II, and 11% of diagnosed as stage III. Fifty percent of patients had myometrial invasion, 9% had cervical invasion, 3% showed serosal invasion, 10% showed lymphovascular invasion, and only 1 patient (0.6%) had neural invasion. After the operation, 11 patients (7%) showed nodal metastasis (Table 1 showed general characteristics).

In the study group, the median albumin level was 4.3 gr/dl; the median hemoglobin level was 13 gr/dl; the median thrombocyte (PLT) count was 260.00 mm<sup>3</sup>, and the median white blood cell (WBC) level was 7100 mm<sup>3</sup>. Lastly, the mean HALP index was 43 (min 10-max 115).

HALP index levels were significantly decreased from FIGO stage I to stage III (mean values were 50, 40, and 27, respectively,  $p=0.0001$ ), shown in Figure 1.

Myometrial invasion absent and less than ½ groups had significantly higher HALP index compared to myometrial invasion more than ½ group (49, 49, and 37, respectively.  $P$  value was 0.001), and shown in Figure 2.

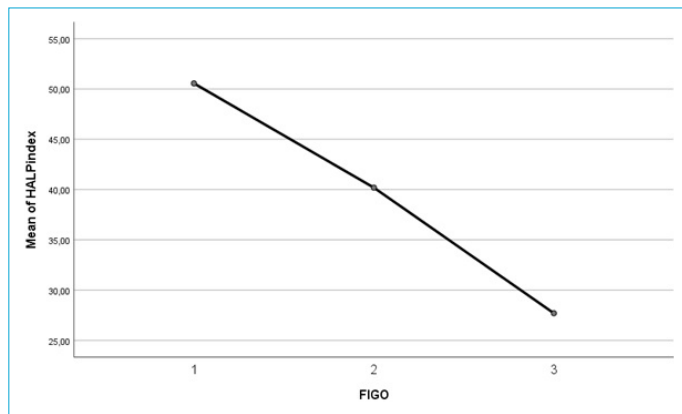
Lymph node metastasis was detected in 11 patients with significantly lower HALP index compared to lymph node-free patients (30 vs 44,  $p=0.018$ ). Patients with lymphovascular invasion showed a significantly lower HALP index than those without invasion (34 vs 44,  $p=0.042$ ). Patients with cervical invasion showed significantly lower HALP index (28 vs 44,  $p=0.002$ ). Lastly, the T stage negatively correlated with HALP index (Pearson Correlation  $-0,25$ ,  $p=0.001$ ).

## Discussion

This study showed that HALP index is a good marker for predicting pathologic features of operable endometrial cancer before the surgery. HALP index significantly decreases with the higher FIGO stage and more invasive tumor, either stromal or vascular side of the tumor tissue.

**Table 1.** General characteristics of the study population

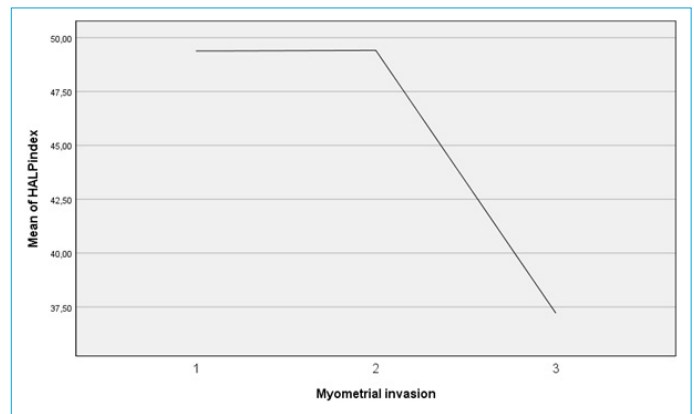
Variable	Mean	Median	Std/IR
Age	61	62	9/41-84
Tumor volume	4	3,5	2,5/0,3-14
Albumine, gr/dl	4,2	4	0,4/3-5
Hemoglobuline, gr/dl	13	13	1,5/9-17
PLT count, mm <sup>3</sup>	263	260	70/60-571
WBC, mm <sup>3</sup>	7400	7100	2500/1,400-23000
HALP index	43	40	18/10-115



**Figure 1.** HALP index and FIGO stage.

Tumor features and anatomical extent are only one factor in the growth and metastasis of cancer. Systemic inflammation and nutrition are known to impact prognosis significantly.<sup>[7]</sup> These two variables are associated with numerous aspects of tumors, such as invasion, proliferation, and metastasis.<sup>[8]</sup> Individually, several inflammatory and dietary variables have been linked to survival rates in some cancer types. The prognostic nutritional index (PNI), the neutrophil-to-lymphocyte ratio (NLR), and the platelet-to-lymphocyte ratio (PLR) are a few instances of how studies have successfully employed a combination of these indicators to predict prognosis with the use of a single index.<sup>[9]</sup> Patients with renal cancer, colorectal cancer, gastric cancer, and bladder cancer were found to correlate with survival and the HALP index, which is computed as Hemoglobin (g/L) Albumin (g/L) Lymphocyte (/L)/Platelet (/L).<sup>[10,11]</sup> The HALP score is a simple-to-replicate instrument that uses routine test values that are widely accessible, so its use in clinical practice could significantly benefit many populations. Regrettably, this index has not yet been verified for endometrial cancer extensively.

Wang et al. recently published a study involving 626 endometrial cancer patients who underwent surgery and discovered that HALP was linked to a decreased risk of endometrial cancer recurrence and mortality. In addition, HALP was a stand-alone protective factor for predicting endometrial cancer death and recurrence. The HALP thresholds for predicting lymph node metastasis (LNM), recurrence, and death are roughly 33.8 for endometrial cancer patients. The recurrence-free and overall survival rates were significantly lower in the low-HALP group than in the high-HALP group. They found that the optimal HALP cutoff values were 33.72, 33.74, and 33.84 for predicting LNM, recurrence, and patient death, respectively.<sup>[12]</sup> This study was the most extensive research, and our findings were similar to these findings. HALP index was 30 in LNM group and 44 in the non-LNM group. Accord-



**Figure 2.** HALP index and Myometrial invasion.

ing to this data, we can speculate that LN dissection or sentinel LN mapping can adjust to the HALP index before the operation.

Another study was published by Njoku et al., and they found that HALP index was linked to unfavorable clinicopathologic variables but not to overall, cancer-specific, or recurrence-free survival. FIGO stage ( $p=0.005$ ), histology ( $p=0.037$ ), disease grade ( $p=0.020$ ), LVSI ( $p=0.027$ ), myometrial invasion ( $p=0.001$ ), recurrence rates ( $p=0.044$ ), and mortality status all showed evidence of a significant correlation with HALP scores.<sup>[13]</sup> Our results were consistent with all these results. Just cut-off values were different, probably due to the population differences.

We have a few major limitations, like the above studies; we could not investigate the oncologic outcomes such as overall and disease-free survivals. But, our primary aim was to determine how this index correlates with pathologic features, so we need a longer follow-up period to clarify these outcomes. There is no data about the relationship between the HALP index and endometrial molecular classification, so we need more prospective research.

In conclusion, this is the first study in our population we found the HALP index is a good prognostic marker to predict pathologic features for early-stage endometrial cancer.

#### Disclosures

**Ethics Committee Approval:** This retrospective study and the Ethics Committee's regulations and the Declaration of Helsinki were followed when conducting the study, which required the confidentiality of patient data to be guaranteed.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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