Observational Study

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The prognostic value of halp score in predicting the efficacy of nivolumab treatment in metastatic malignant melanoma patients

A real-life, retrospective, single center analysis

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Abstract

Patients with metastatic malignant melanoma have a survival rate of less than one year. Nivolumab, a monoclonal antibody against programmed cell death 1 (PD-1) receptor, has improved survival in patients without *BRAF* mutations. The HALP score, calculated from hemoglobin, albumin, lymphocyte, and platelet levels, provides information about a patient immune and nutritional status. High HALP scores have been associated with a better prognosis in various cancers. This study aimed to investigate the effect of high HALP scores on response to nivolumab treatment in patients with metastatic malignant melanoma. A retrospective study was conducted on 44 patients with metastatic malignant melanoma treated with nivolumab at Adana City Training and Research Hospital between 2014 and 2021. Patients who received dabrafenib-trametinib before nivolumab treatment were excluded. The HALP scores were calculated using laboratory parameters before the first nivolumab treatment. Statistical analyses were performed using SPSS version 25.0. The study included 22 female and 22 male patients with a mean age of 61.4 ± 15.6 years. Of the patients, 10 (27.2%) had a positive BRAF mutation, whereas 34 (77.3%) did not. The HALP score cutoff value was determined as 30.1. Patients with high HALP scores had significantly longer progression-free survival (PFS) and overall survival (OS) compared to those with low HALP scores (PFS: median 5.8 vs 3.1 months, $P = .041$; OS: median 54.9 vs 14.4 months, $P = .005$). In this study, we found that high HALP scores were significantly associated with longer PFS and OS in metastatic malignant melanoma patients receiving nivolumab treatment. HALP score was associated with both PFS and OS in patients with metastatic malignant melanoma treated with nivolumab. This immuno-nutritional parameter may be useful in various cancers; however, further prospective studies with larger patient cohorts are needed for clinical application.

Abbreviations: Anti-CTLA-4 = Anti cytotoxic-T-lymphocyte-associated antigen 4, HALP = hemoglobin, albumin, lymphocyte, and platelet, OS = overall survival, PD-1 = programmed cell death 1, PFS = progression-free survival.

Keywords: HALP score, immuno-nutritional parameter, metastatic malignant melanoma, nivolumab, prognosis

1. Introduction

Malignant melanoma is a cancer that develops from melanocyte cells, and ultraviolet radiation is the most important reason for these cells to turn into cancer cells.[1,2] Surgical teatment is the primary treatment for patients with early stage malignant melanoma. Adjuvant treatment is recommended for high-risk patients after surgery.[3–5] The 5-year survival rate after early stage resection is 90%, whereas survival in patients with metastatic disease is less than one year.[6]

In these patients who are resistant to conventional radiotherapy and chemotherapy; the introduction of ICIs targeting CTLA-4, PD-1, and PD-L1, as well as BRAF and MEK inhibitors, has significantly improved outcomes. The current recommended primary medical treatment for metastatic malignant melanoma is the combined use of anti-PD1 and anti cytotoxic-T-lymphocyte-associated antigen 4 (anti-CTLA-4) therapy.[7,8] Since the risk of toxicity is high with this treatment, single-agent anti-programmed cell death protein 1 (anti-PD1) drugs can also

Informed consent was obtained from all participants or legal guardians involved in the study.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Ethical approval for the study was obtained from the Ethics Committee of Adana City Training and Research Hospital with number: 2234.

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be used in the first line.[9] Nivolumab, a monoclonal antibody developed against anti-PD1 receptor, has increased survival in patients without *BRAF* (V-Raf Murine Sarcoma Viral Oncogene Homolog B1) mutations.

Systemic inflammation is known to play a role in the development, growth and metastasis of cancer cells. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score provides information about the patient immune system and nutritional status. Previous studies have demonstrated a correlation between high HALP scores and a good prognosis in different cancer types. In this context, this study aimed to investigate the prognostic value of high HALP scores for predicting the efficacy of nivolumab treatment in patients with metastatic malignant melanoma.

2. Materials and methods

Ethical approval for this retrospective study was obtained from the Ethics Committee of Adana City Training and Research Hospital (date: July 04, 2022, approval number: 2031). The study population consisted of patients registered with the diagnosis of malignant melanoma in the Adana City Training and Research Hospital Medical Oncology Clinic between 2014 and 2021, who received nivolumab treatment for the diagnosis of metastatic malignant melanoma or developed metastases during follow-up and received nivolumab treatment thereafter. Patients who had received dabrafenib and trametinib prior to nivolumab treatment at the metastatic stage were excluded from the study. The study sample comprised of 44 patients (Fig. 1).

HALP scores were calculated based on the following formula, using the results of tests performed on blood samples taken prior to the first nivolumab treatment: hemoglobin level (g/dL) × albumin level (g/dL) × lymphocyte count (/L)/platelet count (/L).

Progression-free survival (PFS) is defined as beginning of nivolumab treatment to disease progression or death from any cause. Overall survival (OS) is defined as beginning of nivolumab treatment to death from any cause.

SPSS 25.0 (Statistical Product and Service Solutions for Windows, Version 25.0, IBM Corp., Armonk, 2017) software package was used to analyze the collected data. Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as mean ± standard deviation and median with minimum-maximum values. Pearson chi-squared test was used to compare categorical variables. The Shapiro–Wilk test was used to analyze the normal distribution characteristics of the variables investigated within the scope of the study. The Mann–Whitney *U* test was used to compare variables that did not conform to the normal distribution. The optimal cutoff value of the HALP score was determined based on the area under the receiver operating characteristic curve. Subsequently, the sensitivity and specificity of the optimal cutoff value of the HALP score were calculated, taking into consideration the mortality data of the patients included in the study. Kaplan–Meier survival analysis was used to analyze patients' recurrence and disease-free survival rates. In determining the relationship between the parameters related to overall survival, the Cox regression test was used in univariate analysis and the multivariate Cox regression test was used in multivariate analysis. Probability (*P*) statistics of ≤.05 were deemed to indicate statistical significance.

3. Results

Of the patients included in the study, 22 (50%) were female, and 22 (50%) were male. The mean age of the patients was 61.4 ± 15.6 years. The number of patients who were positive and negative for *BRAF* mutations was 10 (27.2%) and 34 (77.3%) patients were *BRAF* mutation-positive and-negative, respectively (Table 1). The overall survival (OS) of the patients with positive and negative *BRAF* mutations was 44.1 (min. 18.1, max. 85.1) months and 24.3 (min. 0.01, max. 33) months, respectively (*P* = .201).

While 12 (27.3%) patients transitioned from early to metastatic stage, 32 (72.7%) were metastatic at the time of diagnosis. The optimal cutoff value for the HALP score was determined as 30.1. Patients were divided into 2 groups. Accordingly, patients with HALP scores >30.1 constituted the high HALP score group, and patients with HALP scores <30.1 constituted the low HALP score group.

The median progression-free survival (PFS) and OS of all patients were 4.3 (min. 1.1, max. 10) months and 27.8 (min. 0.01, max. 85.1) months, respectively. The median PFS of the high- and low-HALP score groups was 5.8 (min. 1.6, max. 10) months and 3.1 (min. 1.1, max. 5) months, respectively (*P* = .041; Fig. 2). In addition, the median OS of the high- and low-HALP score groups was 54.9 (min. 24.6, max. 85.1) months and 14.4 (min. 0.01, max. 32.9) months, respectively (*P* = .005; Figs. 3, 4).

In univariate analysis, the relationship between patients' gender, *BRAF* mutation, age and halp score and mean survival was examined using Cox regression test.

In univariate analysis, the relationship between gender, *BRAF* mutation status, age, HALP score, and overall survival was examined using Cox regression test. According to the analysis, it was determined that the age of the patients had a 1.029-fold (OR: 1.029) and a low HALP score had a 2.94-fold (OR: 2.936) effect on mortality (*P* < .05). In multivariate analysis, the ages of the patients and the HALP score cutoff groups that were found to be significant in the univariate analysis were included. It was concluded that the age of the patients had a 1.043-fold (OR: 1.043) effect on mortality; while a low HALP score had a 3.94-fold (OR: 3.944) greater effect on mortality (*P* < .05; Table 2).

4. Discussion

Significant correlations have been reported between HALP score and prognosis in many types of cancers, including breast,

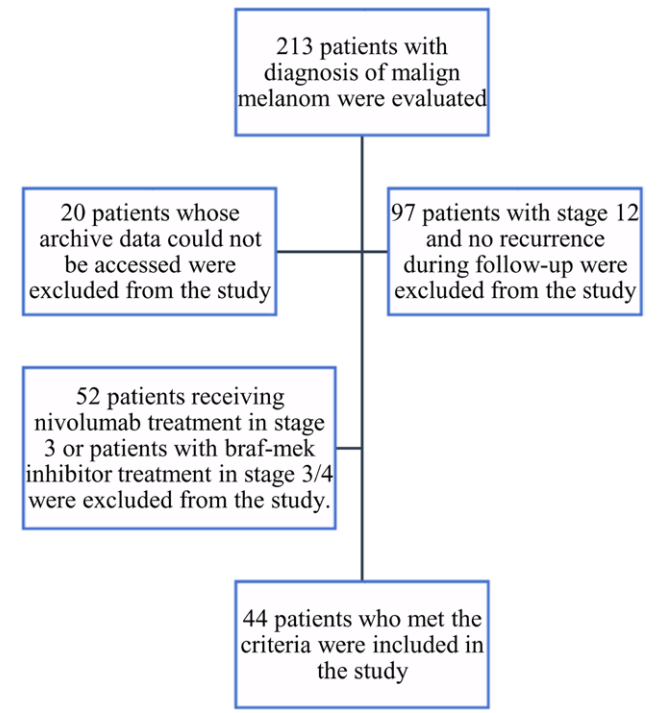

Figure 1. Flow diagram of study.

lung, and prostate cancers.[10–13] The survival rates, which are generally good in the early stages of malignant melanoma, significantly decrease in the metastatic stage. In our study, for the first time in the literature, we investigated the relationship between HALP score and prognosis in metastatic malignant melanoma and found that patients with significantly higher HALP scores had longer progression-free and overall survival rates. In this context, this study was conducted to investigate the relationship between HALP scores and prognosis in metastatic malignant melanoma patients receiving nivolumab treatment. Consequently, patients with significantly higher HALP scores had longer PFS and OS times.

The HALP score was first used by Chen et al in 2015 to predict the prognosis of patients with gastric cancer.[14] Subsequent studies have found a significant relationship between HALP score and prognosis in the bladder, colorectal, prostate, kidney, pharyngeal, esophageal, lung, breast, and cervical cancers.[10,13,15–18] These studies have addressed different types of cancers and different HALP score cutoffs. There was no standard between the stages of cancers and the locations. As a result, the HALP score parameters obtained may vary from cancer to cancer. In order to use this score in clinical practice, different cutoff values should be determined for each type of cancer.

The components of the HALP score are platelet count, lymphocyte count, albumin, and hemoglobin levels. While platelets and lymphocytes show immune status, albumin and hemoglobin show nutritional status and anemia. Cancer patients are at risk for a chronic catabolic state due to both increased metabolic needs and decreased nutrition associated with the side effects of chemotherapy, including vomiting and oral cavity problems. Albumin level, which is affected by metabolic needs and nutritional status, is a simple marker for assessing protein levels. The literature supports the hypothesis that serum albumin levels are significantly associated with cancer survival.[11] Additionally, high albumin levels have been associated with 1-year survival in patients with cancer and cachexia.[19] These findings have also been showed in malign melanoma patients. In a study conducted by Lvm Leek and friends, it was showed that patients with low album values before treatment had shorter OS and PFS.[20] Anemia, which is very common in patients with cancer, can occur through many different mechanisms. In cancer-induced anemia, iron absorption is impaired due to interleukin secretion by T-lymphocytes, erythropoiesis decreases, and malnutrition and chronic blood loss deepen the anemia, negatively affecting the overall process. Anemia may develop in malign melanoma patients due to the reasons mentioned above and this negatively affects survival.[21] The number of platelets increases in cancer patients due to chronic inflammation.[22] High platelet count at the time of diagnosis in melanoma patients increases the risk of metastasis and shortens survival.[23] Increased platelet count negatively affects the prognosis in malign melanoma patients, while increased lymphocyte number positively affects survival in malign melanoma patients.[24]

It has been shown that platelets stimulate angiogenesis via the vascular endothelial growth factors they secrete, enabling cancer cells to escape from the immune system, and thus play a role in the metastasis of cancer cells.[25] Tumor-suppressing effects of lymphocytes are known in both humans and animals.[26] Immune checkpoint inhibitors are known to stimulate the immune system and cause noteworthy treatment responses in some patient subgroups.[27] Although immunotherapy research to date has focused on T cells, B lymphocytes and plasma cells found in the tumor microenvironment have also been shown to play a crucial role in controlling tumors.[28]

Based on the results of studies that addressed the effect of each component of the HALP score separately, the HALP score was used as an immuno-nutritional parameter. Regardless of the use of different HALP cutoff values, all studies found a correlation between high HALP scores and good survival. For example, in a study by Güç et al,

Table 1

Demographic and laboratory characteristics of patients.

	Frequency (n)	Percentage (%)
Gender		
Women	22	50.0
Men	22	50.0
Mortality		
Alive	16	36.4
Exitus	28	63.6
BRAF mutation		
Yes	10	22.7
No	34	77.3
Presence of recurrence		
No	12	27.3
Yes	32	72.7
	Mean ± standard deviation	
Age (yr)	61.4 ± 15.6	
Hemoglobin (gr/dL)	12.4 ± 1.9	
Lymphocyte (/mm^3)	1779.6 ± 970.4	
Albumin (gr/dL)	37.5 ± 5.8	
Platelet count (/mm^3)	292.2 ± 95.8	
C reactive protein (gr/dL)	49.6 ± 59.1	
HALP* score	32.3 ± 17.7	

*HALP: Hemoglobin, albumin, lymphocyte, and platelet.

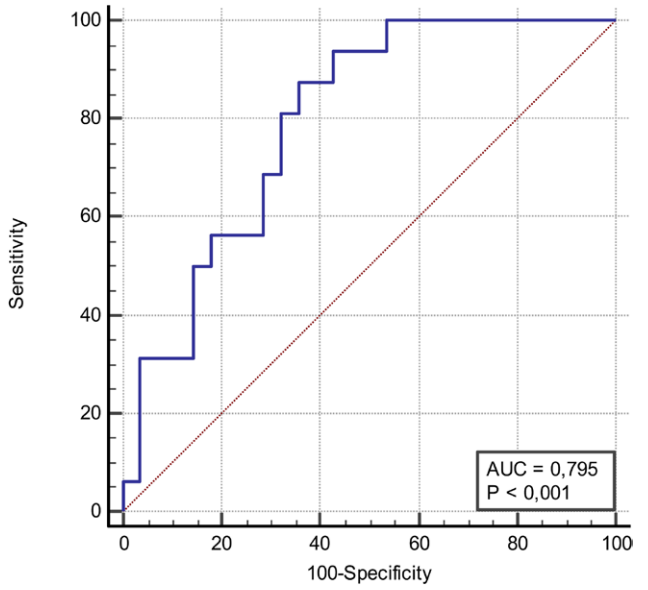

Figure 2. The ROC analysis of HALP score. HALP = hemoglobin, albumin, lymphocyte, and platelet, ROC = receiver operating characteristic.

Table 2

Cox regression test results for analysis of variables.

	Univariate				Multivariate			
			%95 CI				%95 CI	
	P	Exp(B)	Lower	Upper	*P*	Exp (B)	Lower	Upper
Gender	.978	0.989	0.463	2.113				
BRAF mutation	.209	1.872	0.705	4.973				
Age	.042*	1.029	1.001	1.058	.007*	1.043	1.012	1.076
HALP Score	.008*	2.936	1.331	6.475	.002*	3.944	1.683	9240

*$P < .05$, Univariate: Cox regresion test, Multivariate: Multiple Cox regresyon test.

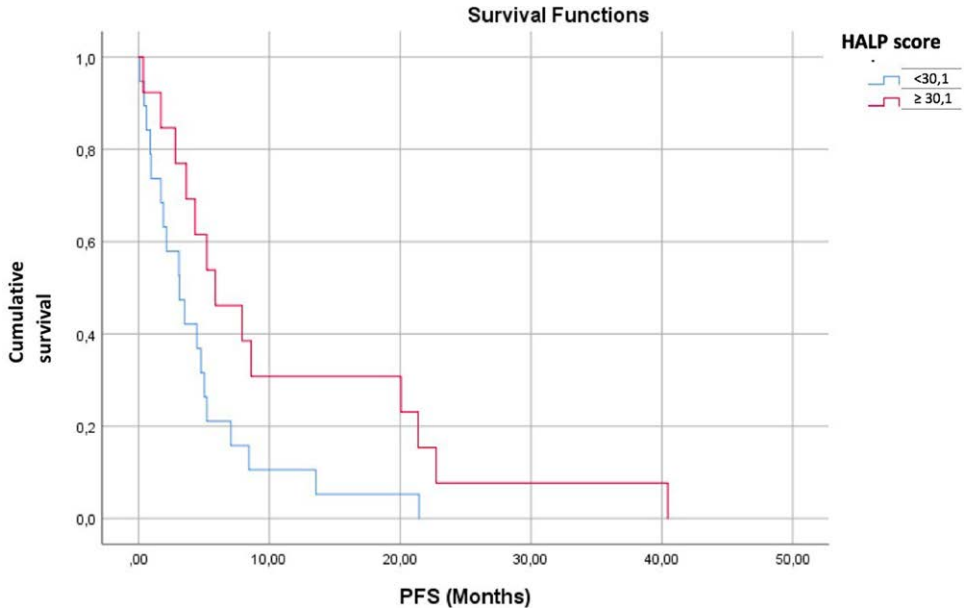

Figure 3. The progression-free survival of patients according to HALP score. HALP = hemoglobin, albumin, lymphocyte, and platelet.

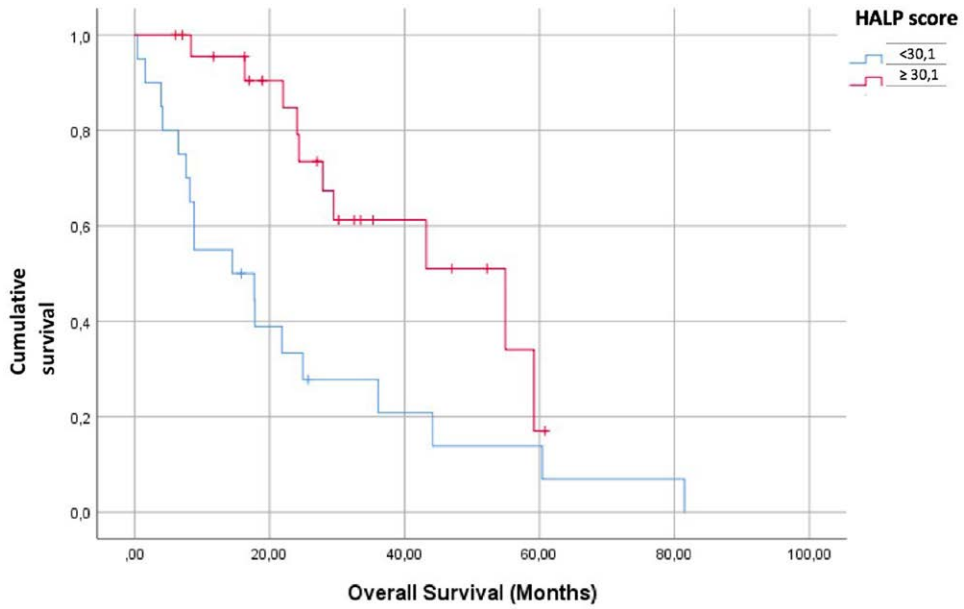

Figure 4. The overall survival of patients according to HALP score. HALP = hemoglobin, albumin, lymphocyte, and platelet.

HALP scores <23.24 were associated with poor prognosis in patients with non-small cell lung cancer.[29] In a study by Gao et al conducted with 533 patients with upper tract urothelial carcinoma undergoing radical nephroureterectomy, the HALP score cutoff value of 28.67 was found to be correlated with both OS and PFS ($P < .001$).[30] In a study of patients with metastatic prostate cancer, Guo et al determined that HALP scores < 32.4 were correlated with shorter PFS and concluded that a low HALP score is an independent risk factor.[31] In a study conducted with 1588 patients with locally advanced cervical cancer, Leetanaporn et al determined that HALP scores > 22.2 were independently associated with better PFS (hazard ratio 0.55) and OS (hazard ratio 0.43).[12] Similarly, in this study, HALP scores < 30.1 were found to be significantly correlated with lower OS and PFS ($P = .005$).

5. Conclusion

In conclusion, the findings of this study, which is the first to investigate the predictive value of the HALP score in malignant melanoma patients using nivolumab at the metastatic stage, revealed significant correlations between the HALP score and PFS and OS. Further prospective large-scale studies are needed to establish the use of the HALP score, which includes immuno-nutritional parameters, in clinical practice for various types of cancer.

6. Limitations

ECOG performance scores of patients could not be evaluated because the data of the patients was accessed from the hospital operating system. The limited number of patients,

the single-center nature of the study and the long observation period are the limitations of our study.

Author contributions

Conceptualization: Serdar Ata, Ali Alper Solmaz, Berna Bozkurt Duman.
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Writing – review & editing: Serdar Ata, Tolga Köşeci, Berna Bozkurt Duman.

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