The Prognostic Value of the HALP Score and Inflammatory Index in Metastatic Castration-Resistant Prostate Cancer Patients Treated with Second-Generation Anti-Androgens

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ABSTRACT

We evaluated the prognostic value of the hemoglobin albumin lymphocyte and platelet (HALP) score and inflammatory index in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with abiraterone and enzalutamide. In this retrospective study, 136 patients with mCRPC were treated with enzalutamide and abiraterone between January 2018 and March 2023; all data were collected from the hospital database. The HALP score and neutrophil-to-lymphocyte ratio (NLR) were calculated from baseline blood tests, and their impacts on progression-free survival (PFS) and overall survival (OS) were analyzed. Patients with lower HALP scores (≤ 23.78) exhibited a significantly reduced OS of 31.2 months compared with those with higher scores (> 23.78, OS: 63.9 months). Similarly, patients with a higher NLR (> 2.15) showed a poorer OS of 38.4 months compared with those with a lower NLR (≤ 2.15, OS: 70.1 months). The results were significant in terms of PFS. Patients with lower HALP scores had a PFS of 22.9 months, whereas those with higher scores had a longer PFS of 43.2 months. For NLR, patients with a score ≤ 2.15 had a PFS of 43.0 months, whereas those with scores > 2.15 had a PFS of 33.5 months. These findings, supported by ROC curve analysis, Kaplan–Meier estimates, and Cox regression analysis, underscore the significance of the HALP score and NLR as prognostic factors. This study highlights the HALP score and NLR as effective, low-cost prognostic markers for patients with mCRPC undergoing treatment with next-generation anti-androgens. These biomarkers can predict patient outcomes and guiding treatment strategies.

Keywords: HALP score, Prostate cancer, Survival

INTRODUCTION

In the field of oncology, prostate cancer (PC) has emerged as a globally prevalent health challenge, ranking fourth among all cancer types in terms of diagnosis frequency.[1] Remarkably, over the past decade, there has been a substantial escalation in the number of prostate cancer cases identified at advanced stages, soaring from 3.9% to 8.2%.[1] This trend highlights the urgent need for enhanced strategies for managing and treating metastatic PC.

Metastatic castration-resistant prostate cancer (mCRPC) is a stage of prostate cancer that has advanced beyond the prostate gland and exhibits resistance to hormonal treatments.[2] For treating mCRPC, several therapies have demonstrated efficacy. These drugs include docetaxel, which is a cornerstone in the management of advanced prostate cancer.[3] In addition, second-generation anti-androgens, such as abiraterone acetate and enzalutamide, have been pivotal in treatment regimens.[4-6] Cabazitaxel is also among the treatment options.[7] However, there remains a lack of unified agreement regarding the sequence of these numerous therapeutic options.

Advancement of cancer is not exclusively influenced by the nature of cancerous cells; factors such as nutrition and immune response also significantly contribute to these mechanisms.[8] The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP score), indicative of immunonutritional status and reflects the overall health of cancer patients, integrates values of hemoglobin, albumin, lymphocytes, and platelets. Use of the HALP score as a prognostic marker in cancer treatment is critical for identifying issues such as nutritional deficiencies, systemic inflammation, and cancer-associated anemia in advanced stages of the disease. In recent cancer research, the HALP score has gained prominence because of its prognostic value in various cancer types.[9] To the best of our knowledge, no studies have evaluated the effectiveness of the HALP score as a prognostic predictor in patients with castration-resistant prostate cancer treated with abiraterone and enzalutamide. Therefore, this study primarily focuses on exploring the prognostic significance of the HALP score in the context of metastatic castration-resistant prostate cancer patients undergoing treatment with abiraterone and enzalutamide, and aims to establish an innovative prognostic model for this patient group.

PATIENTS AND METHODS

This study was a retrospective analysis conducted at Kocaeli University Hospital´s Department of Medical Oncology. Between January 2018 and March 2023, 136 patients diagnosed with metastatic castration-resistant prostate cancer (mCRPC) and treated with enzalutamide or abiraterone were identified.

Data Collection and Parameters

Data on the clinical and pathological features of each patient were collected from the hospital´s database. This encompassed a range of variables, including age, serum PSA levels, Gleason score from biopsies, occurrences of bone and visceral metastasis, dates marking disease progression, performance status as per the Eastern Cooperative Oncology Group (ECOG) scale, albumin levels, and comprehensive blood cell counts. To determine radiological progression in cases of visceral and nodal metastases, the established guidelines from the Response Evaluation Criteria in Solid Tumors (RECIST) were employed. For bone metastasis, progression was identified on the basis of the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria, specifically the emergence of two or more new bone lesions.[10]

The primary goal of this study was to examine the impact of certain parameters, including the HALP score and neutrophil-to-lymphocyte ratio (NLR), on the progression-free survival (PFS) and overall survival (OS) of patients. OS was quantified as the time span from the initiation of enzalutamide or abiraterone therapy until death due to any cause.

In the laboratory analysis, baseline measurements were taken for hemoglobin (Hb), albumin (Alb), lymphocyte count (Lc), and platelet (Plt) levels before the initiation of treatment. The formula for determining the HALP score involved multiplying hemoglobin (Hb in g/L) and albumin (Alb in g/L) levels with lymphocyte count (Lc), and then dividing this product by the platelet count (Pc). NLR was determined by dividing the neutrophil count by the lymphocyte count.

The review board at Kocaeli University Ethical Committee granted ethical clearance for the study, which was conducted in accordance with the principles outlined in the Helsinki Declaration. (Ethical Approval Code: KOU GOKAEK-2023/08.08, Project Identifier: 2023/102).

Statistical Analysis

All statistical analyses were performed using SPSS 20.0 (SPSS, Chicago, IL, USA) and MedCalc 14 (MedCalc Software, Ostend, Belgium). Continuous variables were expressed as either mean±standard deviation or, in cases of non-normal distributions, as median values with interquartile ranges (IQR). Categorical variables are reported as frequencies and percentages. The assessment of continuous variables among various groups was performed using either the independent samples t-test or the Mann–Whitney U test, depending on their suitability. The chi-square test was employed to investigate the relationship between the two categorical variables. To determine the area under the curve (AUC), sensitivity, specificity, and optimal cut-off values, receiver operator characteristic (ROC)

Table 1. Baseline characteristics of the patients

Clinical indexes	n (%)	HALP Score ≤ 23.78 n (%)	HALP Score > 23.78 n (%)
Pre-treatment ECOG performance status			
ECOG 0	41 (32.5)	11 (28.9)	60 (68.1)
ECOG 1	58 (46)	18 (47.3)	21 (23.8)
ECOG 2-3	27 (21.4)	9 (23.6)	7 (7.9)
Bone Metastasis			
None	21 (16.7)	3 (7.8)	18 (20.4)
Present	105 (83.3)	35 (92.1)	70 (79.5)
Visceral Metastasis			
None	104 (82.5)	27 (71.0)	77 (87.5)
Present	22 (17.5)	11 (28.9)	11 (12.5)
Metastatic Tumor Volume			
Low	67 (53.2)	18 (47.3)	49 (55.6)
High	59 (46.8)	20 (52.6)	39 (44.3)
Prior Docetaxel			
None	61 (48.4)	18 (47.3)	43 (48.8)
Present	65 (51.6)	20 (52.6)	45 (51.1)
Second-generation anti-androgens			
Abiraterone	37 (29.4)		
Enzalutamide	89 (70.6)		
HALP Score			
≤ 23.78	38 (30.2)		
> 23.78	88 (69.8)		
NLR			
≤ 2.15	53 (42.1)		
> 2.15	73 (57.9)		

Abbreviations: ECOG= Eastern Cooperative Oncology Group; HALP= hemoglobin, albumin, lymphocyte and platelet; NLR= neutrophilto-lymphocyte ratio

curve analysis was used. Survival analysis was conducted using Kaplan–Meier estimates and the log-rank test in addition to Cox regression analysis. A p-value of 0.05 was indicated statistical significance.

RESULTS

In a retrospective analysis of 126 patients with mCRPC, the median age was 66 (range 41-85 years). Table 1 provides a summary of their characteristics. The median PSA at diagnosis was 88.4 ng/mL (20.27-255 ng/mL); the pretreatment level was 10.34 ng/mL (3.95-44.9 ng/mL). The median follow-up observed was 16 months (IQR 8-27 months). Of the 126 patients, disease progression was detected in 48 (38.1%) and death was observed in 22 (17.5%).

The median HALP score was observed to be 36.9, with a range spanning from 21.9 to 54.3, while the median NLR was recorded at 2.54, ranging between 1.59 and 3.68. ROC analysis was used to determine the ideal threshold values for both the HALP score and NLR. The ROC curve identified an optimal cut-off value of ≤ 23.78 for the HALP score (AUC= 0.756; 95% CI: 0.672-0.828, p< 0.001) and a cut-off value of > 2.15 for NLR (AUC= 0.708; 95% CI: 0.620-0.786, p= 0.001). Subsequently, the 126 patients were stratified into groups based on low and high HALP scores. Similarly, the patients were also stratified based on their NLR results into low and high NLR groups.

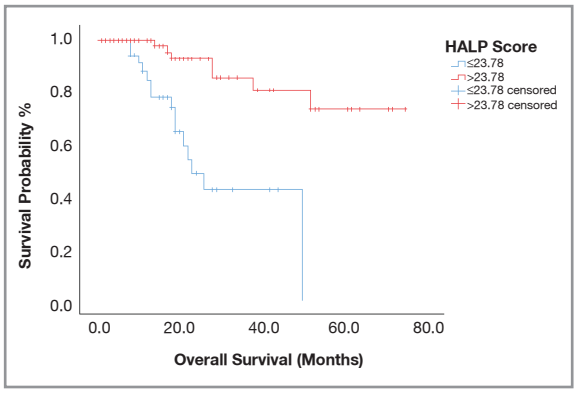

Figure 1. Kaplan-Meier curves of patients based on the HALP score (cut-off value of ≤ 23.78).

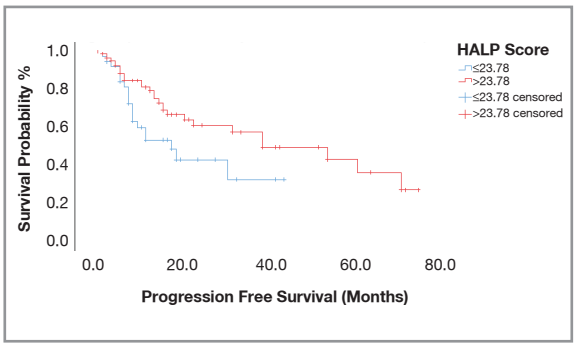

Figure 2. Kaplan–Meier curves of patients based on the HALP score (cut-off value of ≤ 23.78).

At the conclusion of the first year, the anticipated overall survival (OS) rate was 94%. The average OS was 54.1 ± 3.64 months. When considering the HALP score, patients with scores ≤ 23.78 exhibited an OS of 31.2 months ± 3.59, whereas those with scores > 23.78 had a significantly higher OS of 63.9 months ± 3.73 (p< 0.001) (Figure 1). With regard to the neutrophil-to-lymphocyte ratio (NLR), patients with an NLR ≤ 2.15 had an OS of 70.1 months ± 3.3. In contrast, those with an NLR > 2.15 had a considerably lower OS of 38.4 months ± 3.73 (p< 0.001)

Progression-free survival (PFS) rates were observed to be 71% after the first year. The average PFS was documented 39.3 ± 3.54 months. Analyzing based on the HALP score, patients in the ≤ 23.78 group had a PFS of 22.9 months ± 3.13, while those in the > 23.78 group experienced a notably longer PFS of 43.2 months ± 4.20 (p= 0.036), as shown in Figure 2. For NLR values, patients with a score ≤ 2.15 had a PFS of 43.0 months ± 4.9, whereas those scoring > 2.15 had a PFS of 33.5 months ± 4.12, although this difference was not statistically significant with a p-value of 0.169.

In the univariate analysis, among 126 participants, a higher ECOG score (HR= 7.880, 95% CI: 1.668-37.236, p= 0.009), low HALP scores (HR= 6.556, 95% CI: 2.484-17.305, p< 0.001), and elevated NLR (HR= 10.629, 95% CI: 2.463-45.874, p= 0.002) emerged as significant predictors of decreased survival rates (Table 2).

In the Cox multivariate analysis, factors such as high metastatic tumor volume, pre-treatment PSA levels, pre-treatment ECOG status, HALP, and NLR score were examined in terms of their impact on OS. Upon evaluation, it was determined that pre-treatment PSA (HR= 1.001, 95% CI: 1.000-1.003, p= 0.037), pre-treatment ECOG (HR= 5.632, 95% CI: 1.152-27.538, p= 0.033), and a high NLR score (HR= 7.257, 95% CI: 1.489-35.379, p= 0.014) were independently associated with a poorer prognosis for overall survival Table 2.

DISCUSSION

This study underscores the significant prognostic utility of the HALP score and NLR in patients diagnosed with metastatic prostate cancer prior to the initiation of next-generation androgen receptor inhibitor therapies. Our research indicates that a lower HALP score is correlated with shortened PFS and OS. Additionally, an increased NLR is associated with a less favorable prognosis. To the best of our knowledge, our research is among the first to extensively explore the prognostic significance of both the HALP score and NLR indexes in metastatic prostate cancer patients undergoing treatment with next-generation anti-androgens.

The NLR, calculated using the counts of neutrophils and lymphocytes in peripheral blood samples, serves as a marker. Elevated NLR is considered indicative of systemic inflammation. Studies in the literature have consistently demonstrated that high NLR values are associated with poor prognosis in

Table 2. Univariate and multivariate analyses of prognostic factors for OS

	Univariate analysis			Multivariate analysis		
Clinical indexes	**HR**	**(95% CI)**	**p**	**HR****	**(95% CI)**	**p**
Metastatic Tumor Volume						
Low*	1.00			1.00		
High	2.55	0.99-6.53	0.05	2.55	0.89-7.29	0.080
Pre-Treatment PSA	1.00	1.00-1.00	0.08	1.00	1.00-1.00	0.037
Pre-treatment ECOG performance status						
0*	1.00			1		
1	3.08	0.67-14.08	0.146	1.12	0.23-5.40	0.879
2-3	7.88	1.66-37.23	0.009	5.63	1.15-27.53	0.033
NLR						
≤ 2.15*	1.00			1		
> 2.15	10.62	2.46-45.87	0.002	7.25	1.48-35.37	0.014
HALP Score						
≤ 23.78	6.55	2.48-17.30	<0.001	2.55	0.85-7.59	0.093
> 23.78*	1.00			1		

Abbreviations: ECOG= Eastern Cooperative Oncology Group; HALP= hemoglobin, albumin, lymphocyte and platelet; NLR= neutrophilto-lymphocyte ratio
* Reference Category ** Adjusted

certain solid tumor types.[11,12] In this context, the roles of cells in tumor development, the invasive characteristics of the tumor, and the formation of metastasis have been emphasized, and high NLR values have been shown to be a significant determinant of treatment response.[13,14] Our study found that high NLR values in metastatic prostate cancer patients receiving abiraterone and enzalutamide treatments are correlated with poorer overall survival and progression-free survival.

The HALP score, calculated using hemoglobin, albumin, lymphocyte, and platelet values obtained from routine blood tests, is a readily applicable indicator in clinical practice. Recent studies have highlighted its significant correlation with survival durations in patients suffering from renal, bladder, stomach, and lung cancers.[15-18] This index, derived from the product of hemoglobin, albumin, and lymphocyte levels and the ratio of platelet count, stands out as an effective tool for prognosis determination across various cancer types because of its broad accessibility. The strong correlation of the HALP score, particularly with the survival times of patients afflicted with these cancers, can be considered a vital indicator, supporting the clinical significance and advocating for the widespread adoption of this index. Kaya et al. investigated the diagnostic potential of the pre-operative HALP score with PCa and benign prostatic hyperplasia.[19] In contrast, a study conducted by Guo et al. revealed that the HALP score is a significant risk factor for progression-free survival following cytoreductive radical prostatectomy in metastatic PCa patients.[20] Furthermore, Wu et al. demonstrated a substantial correlation between the prognosis of hormone-sensitive prostate cancer and the HALP score.[21] However, the ability of the HALP score to predict disease progression and overall survival in patients with mCRPC treated with next-generation anti-androgens remains unclear. Our study found that the HALP score was significantly correlated with prognosis in patients with metastatic CRPC receiving abiraterone and enzalutamide therapy. These findings aid in a deeper understanding of the role of the HALP score in PCa treatment and support its potential use as a biomarker.

In prostate cancer research employing the HALP index, median values are also used as cut-off points.[19] However, our study adopted a more specific and individualized approach by determining

the HALP index through ROC analysis, rather than relying on median values. This method provided a more accurate and customized prognostic assessment for our patient cohort. As research employing the HALP index expands, the development of a standard cut-off value is expected.

The results of this study should be analyzed while considering some crucial constraints. First, the retrospective approach and the fact that the study was conducted in a single center with a limited patient cohort may introduce potential biases. Thus, to verify our findings, large-scale, prospective investigations are needed. Second, the absence of planned imaging methodologies, which are routinely employed in clinical trials, complicates direct comparisons with clinical trial outcomes. These limitations underscore the need for a detailed and comprehensive review of our research findings before their integration into clinical practice.

In conclusion, the results of this study demonstrate that the HALP index is an effective tool for predicting the prognosis of patients with mCRPC. Notably, the use of this index as a low-cost, rapid, and accurate marker significantly contributes to the determination of prognosis in this patient population. Use of the HALP index can aid in better understanding the response of patients to treatment and disease progression in the management of metastatic castration-resistant prostate cancer. This study, which is among the first in the field, highlights the potential of the HALP index in clinical practice and lays the groundwork for subsequent explorations in this field.

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