HALP Score as a New Prognostic Factor for Patients with Metastatic Bladder Cancer

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ABSTRACT

Objective: To investigate the effect of the haemoglobin, albumin, lymphocyte, and platelet (HALP) score (Haemoglobin, Albumin, Lymphocyte, Platelet count) on survival as a new prognostic factor in metastatic bladder cancer.

Study Design: Descriptive study.

Place and Duration of the Study: Department of Medical Oncology, Celal Bayar University, Manisa, Turkey, and Adnan Menderes University, Aydin, Turkey, from 2010 to 2020.

Methodology: The medical charts of patients with metastatic bladder cancer were reviewed retrospectively. Prognostic value of the HALP score as a marker of overall survival was examined through a receiver operating characteristic (ROC) curve analysis.

Results: The cut-off value for the HALP score in the ROC curve analysis was 29. The median overall survival (OS) was 19 months when the HALP score was less than 29, and the median OS was 40 months when the HALP score was 29 or greater, and this finding was statistically significant (p = 0.003).

Conclusion: The HALP score is closely related to prognosis in metastatic bladder cancer. A high HALP score is associated with better survival outcomes.

Key Words: *HALP score, Metastatic bladder cancer, Overall survival.*

How to cite this article: Acar O, Ayhan M, Demir B, Ekinci F, Aytac A, Erdogan AP. HALP Score as a New Prognostic Factor for Patients with Metastatic Bladder Cancer. *J Coll Physicians Surg Pak* 2023; **33(12)**:1405-1409.

INTRODUCTION

Bladder cancer is the sixth most common form of cancer in the developed countries.[1] Besides, some countries have a higher incidence of bladder cancer than the developed countries. For example, bladder cancer is the 4th most common cancer in Pakistan.[2] Approximately, 75 percent of cases with bladder cancer have no muscle invasion and are treated with transurethral resection (TUR) of the bladder, while the remaining 25 percent have muscle invasion and metastatic bladder cancer (mBC). Cases with muscle invasion are treated with a radical cystectomy, and approximately 45 percent of such cases will later experience local recurrence or distant metastasis.[3] Of the patients with mBC, 5 percent have *de novo* metastatic disease, and 5-year survival is below 15%.[4] Platinum-based chemotherapy is the standard approach to the treatment of metastatic and unresectable bladder cancer.

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Received: March 22, 2023; Revised: August 04, 2023; Accepted: November 20, 2023
DOI: https://doi.org/10.29271/jcpsp.2023.12.1405

The mean overall survival is approximately 15 months with first-line chemotherapy,[5] while mean survival under second--line chemotherapy administered after the platinum-based chemotherapy is low at approximately 6 months.[6]

There is no definitive marker indicating prognosis in mBC, although various markers had been studied for their performance in predicting prognosis, such as neutrophil-to-lymphocyte ratio (NLR), Geriatric Nutritional Risk Index (GNRI), serum C-reactive protein (CRP), and Modified Glasgow Prognostic Score.[7-9] A new marker based on Haemoglobin, Albumin, Lymphocyte, and Platelet counts (HALP score) was developed in the recent years for the prediction of prognosis in cancer patients,[10–14] and its success in predicting prognosis before surgery in patients with early-stage bladder cancer had been tested.[10] There had been no study to explore its utility in cases of mBC. The aim of the present study was to evaluate the performance of the HALP score in cases of metastatic disease in predicting overall survival in patients with *de novo* metastatic disease or in those with metastases that developed later.

METHODOLOGY

The archived records of patients diagnosed with bladder cancer between 2010 and 2020 and regularly attended follow-up visits at Manisa Celal Bayar University Hafsa Sultan Hospital and

Aydin Adnan Menderes University Hospital, Turkey were reviewed retrospectively. Patients with *de novo* metastatic disease and developed metastatic disease after undergoing adjuvant therapy, including radiotherapy, were included in the study. Patients under the age of 18 years and those with two or more primary cancers were excluded. Clinical and pathological patient characteristics such as histological type, receipt of local therapy, history of adjuvant radiotherapy, distant metastasis sites, creatinine, total bilirubin, alkaline phosphatase (ALP), CRP, albumin, haemoglobin, platelet, neutrophil, and lymphocyte were recorded. Patients undergoing treatment were evaluated clinically and radiologically after every three months.

The analysed endpoints of the study were overall survival (OS) and progression-free survival (PFS). The response to treatment was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1. Any clinical findings and side-effects encountered during the therapy were recorded. The HALP score was calculated at the time of metastasis and after the therapy using the formula: Haemoglobin (g/L), Albumin (g/L), Lymphocyte count (count/L) / Platelet count (count/L). The prognostic value of the HALP score as a marker of OS was examined based on a receiver operating characteristic (ROC) curve analysis. Patients were grouped based on BMI scores of below and above 25.

The statistical analysis was conducted in SPSS (Version 16.0. Chicago, SPSS Inc.). Descriptive statistics were presented as numbers and percentages for categorical variables, and continuous variables were presented as mean, standard deviation, and median, and with minimum and maximum values. The cut-off values for the derivate OS and PFS time scores were calculated using X-Tile version 3.6.1 software, as well as for CR/non-CR state done by receiver operating characteristics analysis. The survival analysis involved a log-rank test, and Kaplan-Meier curves were used to illustrate the important variables. Hazard ratios were determined with a Cox regression analysis for multiple variables having estimated prognostic importance. The level of statistical significance was set to an alpha of 0.05 (CI of 0.95).

RESULTS

A total of 145 patients from the two centres were included in the study. Of the patients, 87.6 percent were males, and the median age at diagnosis was 69 (63–75) years. The rate of patients with a BMI of 25 kg/m^2 or greater was 58 percent; 84.1 percent of the patients had a history of smoking; and the Eastern Cooperative Oncology Group (ECOG) performance score was 0–1 in 73 percent of patients. Hypertension and coroner artery disease (CAD) were the most common comorbid conditions, and 89 percent had been diagnosed with bladder cancer based on a transurethral resection (TUR), with the most common histological subtype being urothelial carcinoma (93.8%). The ratio of patients who had undergone intravesical BCG therapy in the disease period without muscle invasion was 15.9 percent. Of these patients, 16.6 percent were treated with radiotherapy for the local disease. The most common metastasis site was the lung. The ratios of patients receiving first-line, second-line, and third-line systemic therapies were 47 percent, 23 percent, and 11 percent, respectively (Table I).

The cut-off point for the HALP score in the ROC curve analysis was 29. Of the sample, 89 patients were below (61%) and 56 (39%) were above this cut-off. According to the results of the Kaplan-Meier survival analysis and log-rank test, the median OS was 19 months when the HALP score was less than 29, and the median OS was 40 months when the HALP score was 29 or greater. This finding was statistically significant ($p = 0.003$).

When the subgroups were examined in high HALP score for overall survival with a univariate analysis, overall survival was found to be significantly longer in patients with a BMI of 25 or greater, in the presence of comorbid disease, in those who underwent radiotherapy, and in those who received the local therapy to the bladder in the disease period when muscle invasion was not present (p=0.004, 0.032, 0.003, and 0.002, respectively; Table II).

Table I: Clinical and demographic characteristics of patients (n=145).

Age (Median (IQR)	69 (63–75)
BMI ≥24, n (%)	85 (58.6)
Gender, n (%)	
Female	18 (12.4)
Male	127 (87.6)
ECOG-PS, n (%)	
0–1	106 (73.1)
2	31 (21.4)
3–4	8 (5.5)
Smoking, n (%)	
Never smoker	23 (15.9)
Former smoker	83 (57.2)
Current smoker	39 (26.9)
Comorbidity, n (%)	
HT	70 (48.3)
DM	26 (17.9)
CAD	37 (25.5)
COPD	18 (12.4)
Type of diagnosis, n (%)	
Total cystectomy	14 (9.7)
Partial cystectomy	2 (1.4)
TUR-B	129 (89.0)
Histological type, n (%)	
Urothelial carcinoma	136 (93.8)
Other	9 (6.2)
Receipt of local therapy, n (%)	
No	64 (44.1)
TUR-B	58 (40.0)
TUR-M and intracavitary BCG	23 (15.9)
Radiotherapy	39 (26.9)
Adjuvant therapy, n (%)	24 (16.6)
Metastasis sites, n (%)	
Liver	26 (17.9)
Lungs	63 (43.4)
Bone	51 (35.2)
Number of metastatic lines	
1st line	69 (47.6)
2nd line	34 (23.4)
3rd line	16 (11.0)
4th line	2 (1.4)
5th line	0
6th line	1 (0.7)

ECOG: Eastern Cooperative Oncology Group, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, TUR-B; Transurethral resection-bladder.

Table II: OS for clinical and demographic features.

	Univariate analysis					Multivariate analysis		
	Total n	No. of events	Median	95% CI	p-value	Exp (B)	95% CI	p-value
Age								
<65	49	31	28.0	15.43–40.56	0.094			
≥65	96	66	21.0	12.86–29.13				
Smoking								
No	23	15	16.0	12.16–19.83	0.892			
Yes	122	82	25.0	19.59–30.40				
BMI_class								
<24	60	45	18.0	11.45–24.54	0.004	1.627	1.031-2.426	0.036
≥24	85	52	33.0	18.06–47.94				
Comorbidities								
No	52	35	16.0	9.39–22.60	0.032	1.451	0.939–2.250	0.093
Yes	93	62	28.0	16.04–39.95				
Histological type								
Urothelial carcinoma	136	92	24.0	18.91–29.09	0.924			
Other	9	5	19.0	5.90–32.09				
Receipt of RT								
No	106	71	20.00	12.67–27.32		1.881	1.150–3.015	0.011
Yes	39	26	42.00	20.11–63.88	0.003			
Adjuvant therapy								
No	121	76	21.0	13.86–28.13	0.201			
Yes	24	21	34.0	16.84–51.15				
Local therapy								
No	64	38	13.0	9.48–16.51	0,002	1.542	1.018–2.509	0.042
Yes	81	59	33.0	22.37–43.62				

OS: Overall survival, BMI: Body mass index, RT: Radiotherapy.

Table III: PFS for clinical and demographic features.

	Univariate analysis					Multivariate analysis		
	Total n	No. of events	Median	95% CI	p-value	Exp (B)	95% CI	p-value
Age								
<65	49	45	12.0	0.54–23.45	0.121			
≥65	96	87	2.0	0.00–4.40				
Gender								
Male	127	120	4.0	0.00–8.51	0.411			
Female	18	16	0.0	0.00-0.00				
Smoking								
No	23	21	8.0	0.00–16.45	0.194			
Yes	122	115	2.0	0.00–4.74				
BMI class								
0.00	60	59	1.00	0.00–0.00	0.010	1.325	0.927–1.893	0.123
1.00	85	77	8.00	0.00–16.24				
Comorbidities								
No	52	49	2.00	0.00–4.90	0.164			
Yes	93	87	3.00	0.00–8.32				
Histological type								
Urothelial carcinoma	136	127	4.00	0.00–8.63	0.172			
Other	9	9	0.00	0.00-0.00				
Receipt of RT								
No	106	98	0.00	0.00-0.00	0.002	1.474	0.983–2.209	0.061
Yes	39	38	13.00	3.21-22.78				
Adjuvant therapy								
No	121	112	1.00	0.00-0.00	0.008	1.323	0.826–2.118	0.244
Yes	24	24	16.00	11.19-20.80				
Local								
No	64	60	0.00	0.00-0.00	<0.001	2.996	1.974–4.545	<0.001
Yes	81	76	16.0	12.19-19.80				

PFS: Progression free survival, BMI: Body mass index, RT: Radiotherapy.

In the multivariate analysis, overall survival was found to be significantly longer in patients with a BMI of 25 or greater in those who underwent radiotherapy and who received the local therapy (p=0.036, 0.011, and 0.042, respectively; Table II).

In the analysis of progression-free survival based on univariate analysis in high HALP score, PFS was significantly longer in patients with a BMI of 25 or greater, in those who underwent radiotherapy, in those who received adjuvant therapy, and in those who received the local therapy to the

bladder in the disease period when muscle invasion was not present (p=0.010, 0.002, 0.008, and <0.001, respectively; Table III). In the multivariate analysis, PFS was significantly longer only in patients who received the local therapy to the bladder (p<0.001; Table III).

DISCUSSION

The previous studies had established a clear relationship between nutritional status and systemic inflammatory response, and the onset, progression, and metastasis of cancer.[15] The HALP score has been developed recently as a novel marker of nutritional and inflammatory status. Anaemia evaluated from the haemoglobin component of the HALP score is common in cancer patients and can occur as a result of iron deficiency, folic acid deficiency, vitamin B12 deficiency, chemotherapy side effects, and inflammatory processes. Some past studies had reported performance status and survival outcomes to be poorer in patients with anaemia ahead of cancer therapy.[16,17] Albumin, the second component of the HALP score, is a negative acute phase reactant synthesised in the liver. Albumin can decrease during inflammatory conditions, including cancer, and levels can offer a clear indication of nutritional status.[18] Among the components of the HALP score, lymphocytes and platelets are involved in inflammation in the microenvironment of tumour cells. Lymphocytes can cause the death of tumour cells by secreting tumour necrosis factor alpha (TNF-a) and interferon gamma, and a decreased lymphocyte count can influence disease progression and be linked to poor survival outcomes.[19] Increasing the number and activation of platelets can induce tumour growth. Platelets adhering to tumour cells increase endothelial permeability by releasing vascular endothelial growth factor (VEGF), inducing neo-angiogenesis, and this can cause metastasis and disease progression.[20]

Based on these observations, haemoglobin, albumin, and lymphocyte show a positive correlation and platelet count shows a negative correlation. Previous studies had proposed the use of the HALP score for the prediction of prognosis in various cancers.[21–24] Peng *et al.* examined the use of the HALP score for the prediction of prognosis ahead of radical cystectomy in patients with bladder cancer,[10] studying the complete blood count and biochemical parameters of 516 patients scheduled for cystectomy. The study reported a HALP score of 22 to be predictive, while overall survival was lower in patients with a low HALP score, to a statistically significant degree. The authors also further reported lower HALP scores in patients aged above 65 years, in females and in those with a high T stage.

However, there had been no study to evaluate the HALP score in mBC, and the present study, thus, proposed a new prognostic marker for survival. In this study, overall survival was significantly higher in patients with a high HALP score (40 months *vs*. 19 months, p = 0.003). In the univariate analysis with a high HALP score, the overall survival was statistically significantly higher in patients with a high BMI, those with comorbid disease, and those treated previously with radiotherapy or local therapy. Higher HALP scores in patients with a high BMI can be explained by the absence of cachexia and the resulting high albumin levels in this group of patients. Similarly, higher HALP scores were noted in the subgroup of patients who had previously undergone radiotherapy or the local therapy, which suggested that poor survival outcomes may be observed in patients with *de novo* metastatic disease.

Among the limitations of the present study was the lack of a clear cut-off point for the HALP score, so different studies can produce different results. Nonetheless, the authors recommended the calculation of the HALP score while diagnosing metastatic bladder cancer, since it is a non-invasive, cost-effective, practical, and easily accessible measure. One strength of the present study was its inclusion of two different hospitals. However, the retrospective design of the study can reduce its reliability due to the possibility of biases.

CONCLUSION

The HALP score is closely related to prognosis in metastatic bladder cancer. A high HALP score is associated with better survival outcomes. Despite the lack of a definitive cut-off point, the authors would recommend the use of HALP score in patients with metastatic bladder cancer due to its low cost and ease of application.

ETHICAL APPROVAL:
The study was granted approval by the Health Sciences Ethics Committee of Manisa Celal Bayar University, Faculty of Medicine with decision number 244, dated 10 January, 2022.

PATIENTS' CONSENT:
Due to retrospective nature of the study, explicit consent of patients was not required.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
FE: Drafting the work and revising for intellectual content.
MA, BD, AA: Interpretation and data analysis for the manuscript.
APE: Interpretation of data and final approval of version to be published.
OA: Drafting and revision of the work critically for final publication, accountable for all aspects of work.
All authors approved the final version of the manuscript to be published.

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