

Efficacy of the HALP Score in Predicting Progression in Patients Undergoing Radical Cystectomy for Muscle Invasive Bladder Cancer

Rıdvan Kayar¹, Kemal Kayar², İlker Artuk², Samet Demir², Emre Tokuç³, Metin İshak Öztürk¹

¹ Department of Urology, University of Health Science, Van Training and Research Hospital, Van, Türkiye

² Department of Urology, Haydarpaşa Numune SUAM, University of Health Science, İstanbul, Türkiye

³ Department of Urology, Medical Park Göztepe Hospital Complex, Bahçeşehir University, İstanbul, Türkiye

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Corresponding Author;

Rıdvan Kayar, M.D.

Address: SBU Van Training and Research Hospital, Urology, Van, Türkiye

E-mail: dr.ridvankayar@gmail.com

ORCID

R.K. [0000-0002-1765-919X](https://orcid.org/0000-0002-1765-919X)

K.K. [0000-0003-0731-9877](https://orcid.org/0000-0003-0731-9877)

İ.A. [0000-0002-7889-4943](https://orcid.org/0000-0002-7889-4943)

S.D. [0009-0006-5333-134X](https://orcid.org/0009-0006-5333-134X)

E.T. [0000-0002-5885-9278](https://orcid.org/0000-0002-5885-9278)

M.İ.Ö. [0000-0002-1868-2316](https://orcid.org/0000-0002-1868-2316)

Abstract

Objective: This study investigated the prognostic value of the HALP score, comprising haemoglobin, albumin, lymphocyte, and platelet parameters, on progression and progression-free survival (PFS) in patients undergoing radical cystectomy (RC) for non-metastatic muscle-invasive bladder cancer (MIBC).

Material and Methods: A retrospective analysis was conducted on 134 MIBC patients who underwent RC between February 2014 and January 2024. The HALP score was calculated using the formula: HALP = (haemoglobin × albumin × lymphocytes) / platelets. Associations between HALP score, clinicopathological parameters, progression, and PFS were assessed via Kaplan-Meier survival analysis, ROC curve analysis, and multivariate logistic regression.

Results: The median HALP score was significantly lower in patients with disease progression (29.19 [IQR: 19.17–41.81]) compared to those without progression (37.55 [IQR: 29.61–52.25]; $p = 0.021$). Patients with a HALP score <36.38 had a mean PFS of 68.8 months (95% CI: 52.6–85.1), compared to 82.4 months (95% CI: 66.5–98.2) in patients with a HALP score ≥ 36.38 ($p=0.021$). ROC analysis yielded an AUC of 0.619 (95% CI: 0.518–0.721) for predicting progression, with sensitivity and specificity of 54.9% and 55.4%, respectively. Perineural invasion (PNI) emerged as an independent prognostic factor for progression (OR=2.56, 95% CI: 1.011–6.482, $p=0.047$), and low preoperative albumin levels significantly increased progression risk ($p=0.032$).

Conclusions: Although the HALP score is a statistically significant prognostic marker for predicting progression in patients with MIBC, it has limited predictive power. Our results demonstrate the potential of the HALP score as a helpful tool in individualised treatment approaches. However, the prognostic value of the HALP score needs to be confirmed in prospective and multicentre studies in larger patient populations.

Keywords: HALP score, muscle invasive bladder cancer, progression, radical cystectomy

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INTRODUCTION

Bladder cancer (BC) is the tenth most common malignancy worldwide and the thirteenth leading cause of cancer-related mortality. Exposure to environmental and occupational chemicals is an important risk factor in the aetiology of BC and the most prominent carcinogen is tobacco smoke (1). Radical cystectomy (RC) is considered the gold standard treatment for non-metastatic muscle-invasive bladder cancer (MIBC) (2).

Types of recurrence after RC include local recurrence and distant metastases (lymph nodes, lung, liver and bone). The main epidemiological factors predicting recurrence after RC are advanced age, female sex and tobacco use. In pathological evaluation, the presence of lymphovascular invasion (LVI), concomitant carcinoma in situ (CIS), positive surgical margin and lymph node involvement are considered important prognostic factors for tumour recurrence. On radiological examination cT3-T4a disease and the presence of hydronephrosis are considered independent predictors of poor clinical outcome after RC (3,4).

Anemia, hypoalbuminemia (< 3.5 g/dL), low neutrophil-to-lymphocyte ratio and low lymphocyte-to-monocyte ratio have been observed as markers predicting recurrence in MIBC patients undergoing RC (5–7). The HALP score has been evaluated in several studies as an independent prognostic factor predicting survival in urologic cancers. Lower HALP scores have been significantly associated with poorer overall survival in cancers such as bladder, renal cell carcinoma and upper urinary tract urothelial carcinoma (8). There are few studies in the literature on the prognostic value of HALP score in predicting progression in MIBC patients undergoing RC. In our study, we aimed to evaluate the significance of the HALP score in determining the risk of progression.

MATERIAL AND METHODS

Our study included a total of 205 patients who underwent RC for non-metastatic MIBC between February 2014 and January 2024. A total of 71 patients were excluded from the study. Among them, 32 patients received neoadjuvant chemotherapy before surgery, which can significantly alter pathological staging and systemic inflammatory parameters, potentially confounding the prognostic value of the HALP

score. Additionally, 23 patients had a secondary malignancy. Six patients with acute urinary tract infections and two patients with a history of acquired immunodeficiency were also excluded, as active infection or immunosuppressive conditions may significantly affect hematologic and nutritional biomarkers, thereby distorting the HALP score and compromising the validity of our prognostic evaluation. Furthermore, 8 patients were excluded due to incomplete follow-up at external healthcare centers. After these exclusions, the remaining 134 patients constituted the final analysis cohort.

Demographic and clinical characteristics of the patients included age, sex, comorbidities and smoking. Biochemical data including C-reactive protein (CRP, mg/L), albumin (g/L) and complete blood count parameters [haemoglobin (g/L), lymphocytes ($10^9/L$)] were measured and recorded two weeks prior to surgery. From these data, the HALP score was calculated using the following formula: $[\text{haemoglobin (g/L)} \times \text{albumin (g/L)} \times \text{lymphocytes (/L)}] / \text{platelets (/L)}$.

Clinicopathological data were also collected from the hospital database. These data included date of RC, tumour T and N stages, presence of concomitant CIS and prognostic factors such as LVI and perineural invasion (PNI).

Patients were systematically analysed for the presence of recurrence based on available radiological imaging and multidisciplinary uro-oncology board assessments performed during follow-up. Disease progression was specifically categorized as local recurrence, distant metastasis (lymph nodes, lung, liver, or bone), or both. Progression times (if any) and progression-free survival (PFS) times of patients with progression during follow-up were calculated in months and follow-up periods were recorded as a minimum of 8 months and a maximum of 130 months.

The analyses aimed to evaluate the prognostic effects of the HALP score on disease progression and PFS. Furthermore, the associations of HALP score with important clinicopathological factors such as tumour stage (T and N stages), LVI, PNI and the presence of concomitant CIS were extensively investigated.

Our study was approved by the Scientific Research Ethics

Committee of Haydarpaşa Numune Training and Research Hospital on December 17, 2024, with decision number HNEAH-GOAEK/KK/2024/159. Full compliance with the Declaration of Helsinki was ensured, and written informed consent was obtained from all patients enrolled in the study, who agreed to the anonymous use of their data.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25 software (IBM Corp., Armonk, NY, USA). Continuous variables are presented as median Interquartile Range (IQR), and categorical variables are presented as frequencies and percentages. Mann-Whitney U test was used for group comparisons, ROC curve analysis was used for prognostic assessment and area under the curve (AUC) was calculated. The optimal cut-off point was determined using the Youden index.

Survival analyses were performed using the Kaplan-Meier method and groups were compared using the log-rank test. PFS was evaluated in months and the significance level was accepted as $p < 0.05$. Chi-squared test was used to compare categorical variables and multivariate logistic regression analysis was used to identify independent prognostic factors.

RESULTS

During the clinical follow-up of patients who underwent RC, disease progression was observed in 51 patients (38%). The median age was 66 years [IQR: 60–71] in the progression group and 65 years [IQR: 59–71] in the non-progression group, with no statistically significant difference ($p = 0.793$). The sex distribution was similar between the groups, with males comprising 86% of the progression group and 89% of the non-progression group ($p = 0.617$). A smoking history of ≥ 20 pack-years was present in 78% of patients with progression and in 83% of those without, which did not yield statistical significance ($p = 0.792$). Likewise, the presence of diabetes mellitus ($p = 0.238$), hypertension ($p = 0.886$), and coronary artery disease ($p = 0.963$) showed no significant differences between the groups.

Pathological evaluation revealed that advanced tumor stages (T3–T4) were significantly more frequent in the progression

group (90% vs. 65.1%, $p = 0.001$). When assessed by individual T stage, T2a and T2b tumors were more prevalent among non-progressing patients, whereas T3b and T4a tumors were predominantly observed in those with progression ($p = 0.016$). PNI was significantly associated with progression and was present in 82% of the progression group compared to 54% of the non-progression group ($p = 0.001$). Conversely, lymph node involvement ($p = 0.659$), N stage distribution ($p = 0.585$), concomitant CIS ($p = 0.741$), and LVI ($p = 0.281$) did not demonstrate statistically significant associations with disease progression (Table 1). Advanced tumour stage (T3–T4) emerged as the most decisive factor associated with disease progression, highlighting its significant prognostic importance in this study.

Among the preoperative hematological and biochemical parameters evaluated, patients with disease progression had significantly lower HALP scores compared to those without progression (29.19 [IQR: 19.17–41.81] vs. 37.55 [IQR: 29.61–52.25], $p = 0.021$). Similarly, serum albumin levels were significantly reduced in the progression group (4.0 [IQR: 3.5–4.23] vs. 4.1 [IQR: 3.8–4.3], $p = 0.032$), suggesting a potential association between poor nutritional/inflammatory status and adverse outcomes. In contrast, no significant differences were observed in hemoglobin ($p = 0.512$) or lymphocyte counts ($p = 0.973$) between the two groups. However, platelet counts were modestly higher in patients with progression (290 [IQR: 232–358] vs. 256 [IQR: 217–316], $p = 0.048$), indicating a possible link between elevated thrombocyte levels and tumor progression (Table 2).

According to the results of the ROC curve analysis evaluating the ability of the HALP score to predict progression, the area under the curve (AUC) was calculated as 0.619 (95% CI: 0.518–0.721) and found to be statistically significant ($p = 0.021$). As a result of the analysis, the optimal cut-off point was determined to be 36.38, and at this value, the sensitivity and specificity of the HALP score in predicting progression were 54.9% and 55.4% respectively. These data show that the HALP score has a limited but statistically significant predictive value in predicting the risk of progression (Table 3, Figure 1).

Table 1. Association of Clinical and Pathologic Characteristics with Progression in Patients Undergoing Radical Cystectomy for Muscle Invasive Bladder Cancer

Continuous Variables (Median [IQR])	Progression (+) (n=51)	Progression (-) (n=83)	p
Age	66 (60-71)	65 (59-71)	0.793**
Categorical Variables (n, %)			
Sex			0.617*
Female	7 (13.7%)	9 (10.8%)	
Male	44 (86.3%)	74 (89.2%)	
Smoking			0.792*
-	3 (5.9%)	4(4.8%)	
<20 package/years	8 (15.7%)	10 (12%)	
≥20 package/years	40 (78.4%)	69 (83.1%)	
DM			0.238*
-	42 (82.4%)	61 (73.5%)	
+	9 (14.6%)	22 (26.5%)	
HT			0.886*
-	27 (52.9%)	45 (54.2%)	
+	24 (47.1%)	38 (45.8%)	
CAD			0.963*
-	41 (80.4%)	67 (80.7%)	
+	10 (19.6%)	16 (19.3%)	
T Stage			0.016*
T2a	2 (3.9%)	17 (20.5%)	
T2b	3 (5.9%)	14 (14.5%)	
T3a	11 (21.6%)	15 (18.1%)	
T3b	21 (41.2%)	18 (21.7%)	
T4a	14 (27.4%)	19 (22.9%)	
T4b	0 (0%)	2 (2.4%)	
T Subgroup			0.001*
T2	5 (9.8%)	29 (34.9%)	
T3-4	46 (90.2%)	54 (65.1%)	
Lymph Node Involvement			0.659*
N-	30 (58.8%)	52 (62.7%)	
N+	21 (41.2%)	31 (37.3%)	
N Stage			0.585*
N0	30 (58.8%)	52 (62.7%)	
N1	6 (11.8%)	14 (16.9%)	
N2	14 (27.5%)	15 (18.1%)	
N3	1 (2.0%)	2 (2.4%)	
CIS			0.741*
-	34 (66.7%)	53 (63.9%)	
+	17 (33.3%)	30 (36.1%)	
PNI			0.001*
-	9 (17.6%)	38 (45.8%)	
+	42 (82.4%)	45 (54.2%)	

LVI			0.281*
-	24 (47.1%)	47 (56.6%)	
+	27 (52.9%)	36 (43.4%)	

DM: Diabetes Mellitus, HT: Hypertension, CAD: Coronary Arterial Disease, CIS: carcinoma in situ, LVI: Lymphovascular Invasion, PNI: Perineural Invasion, *: Chi-square, **: Mann-Whitney U test

Table 2. Relationship of Hematologic and Biochemical Parameters with Progression in Patients Undergoing Radical Cystectomy for Muscle Invasive Bladder Cancer

	Progression (+) (n:51) (Median [IQR])	Progression (-) (n:83) (Median [IQR])	p
Halp score	29.19 (19.17-41.81)	37.55 (29.61-52.25)	0.021**
Albumin (g/dl)	4 (3.5-4.23)	4.1 (3.8-4.3)	0.032**
Haemoglobin (g/dl)	11.8 (10.6-13.5)	12.3 (10.9-13.5)	0.512**
Lymphocytes (10³/μl)	1.99 (1.33-2.88)	1.98 (1.62-2.5)	0.973**
Platelets (10³/μl)	290 (232-358)	256 (217-316)	0.048**

** : Mann-Whitney U test

Table 3. ROC Analysis Result of HALP Score According to Progression

	Progression (+) (n:51) (Median [IQR])	Progression (-) (n:83) (Median [IQR])	p
Halp score	29.19 (19.17-41.81)	37.55 (29.61-52.25)	0.021**
Albumin (g/dl)	4 (3.5-4.23)	4.1 (3.8-4.3)	0.032**
Haemoglobin (g/dl)	11.8 (10.6-13.5)	12.3 (10.9-13.5)	0.512**
Lymphocytes (10³/μl)	1.99 (1.33-2.88)	1.98 (1.62-2.5)	0.973**
Platelets (10³/μl)	290 (232-358)	256 (217-316)	0.048**

** : Mann-Whitney U test

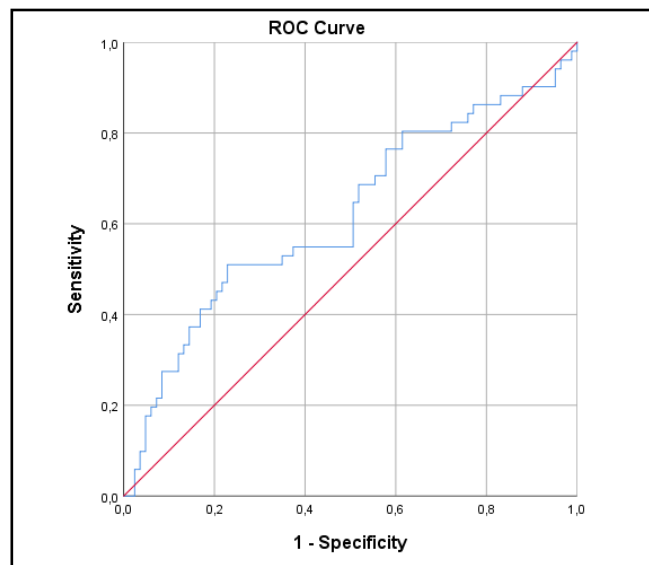


Figure 1. ROC Analysis Result of HALP Score According to Progression

Logistic regression analysis in our study group revealed that T subgroup (OR=3.09, 95% CI: 1.00-9.564, p=0.050) and perineural invasion (OR=2.56, 95% CI: 1.011-6.482, p=0.047) variables showed statistical significance as independent and strong prognostic markers in predicting muscle invasive bladder cancer progression. Although the HALP score cut-off point was not statistically significant (OR=0.65, 95% CI: 0.31-1.369, p=0.258). The overall fit of the model was supported by a -2 log-likelihood value of 160.936 and Nagelkerke R²=0.163, which reasonably reflects the explanatory power of the model. ROC curve analysis evaluated the classification performance of the model and the AUC value was 0.705 (Table 4, Figure 2).

There was no statistically significant difference between groups for local recurrence, distant metastasis and both

progression types in the distribution of progression types according to the HALP score cut-off point of 36.38 ($p=0.859$) (Table 5).

According to the results of the Kaplan-Meier survival analysis, when PFS times were compared according to the HALP score cut-off point of 36.38, the mean survival time was 82.4 months (95% CI: 66.5-98.2) in the group of patients with HALP score ≥ 36.38 and 68.8 months (95% CI: 52.6-85.1) in the group with HALP score < 36.38 (Figure 3).

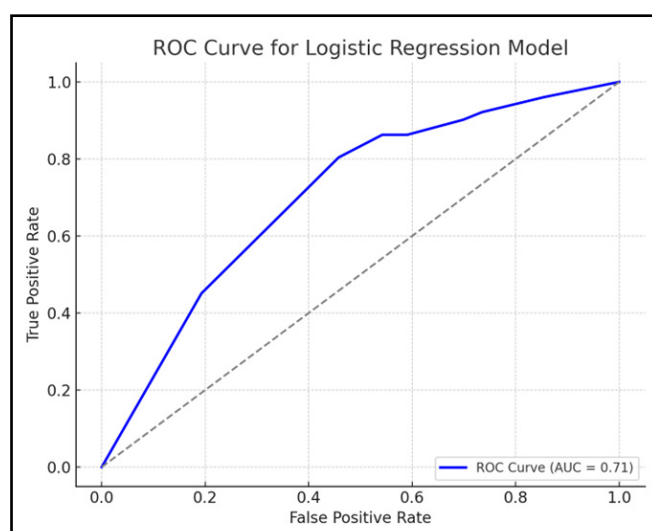


Figure 2. ROC Curve for Logistic Regression Model Predicting Muscle-Invasive Bladder Cancer Progression

DISCUSSION

MIBC is a crucial malignancy that requires a multidisciplinary approach due to its high mortality rate and aggressive clinical course. Therefore, accurate and reliable identification of prognostic markers may improve patient management by contributing to the development of individualised treatment approaches. This study aimed to add unique and clinically relevant findings to the literature by comprehensively evaluating the prognostic value of the HALP score for disease progression and survival.

Pathological factors remain integral in determining the prognosis of muscle-invasive bladder cancer. In our study, while pT stage exhibited a strong association with recurrence, LVI and pathological nodal status (pN stage) did not demonstrate statistically significant predictive value for progression. Notably, PNI emerged as the most robust independent prognostic marker for recurrence, suggesting its potential to enhance existing prognostic models for bladder cancer progression. This finding aligns partially with the work of Karakiewicz et al., who identified pathological staging and LVI as powerful predictors of recurrence but contrasts with Lotan et al., who found no significant association between LVI and recurrence. These discrepancies underscore the variability in the prognostic relevance of LVI across studies and highlight the need for further investigation (10,11).

Table 4. Logistic Regression Analysis Results in Predicting Muscle Invasive Bladder Cancer Progression

Variables	B	SE	OR	CI	Z	p
Halp Score	-0.429	0.379	0.65	0.65 (0.31-1.369)	-1.132	0.258
T Subgroup	1.129	0.576	3.09	3.09 (1.0-9.564)	1.96	0.050
PNI	0.940	0.474	2.56	2.56 (1.011-6.482)	1.983	0.047

Table 5. Statistical Distribution of Progression Types According to HALP Score

Progression Type	HALP Score < 36.38	HALP Score ≥ 36.38	p*
Local Recurrence	5 (%10)	3 (%6)	0.859
Distant Metastasis	17 (%33)	14 (%28)	
Both Local Recurrence and Distant Metastasis	6 (%12)	6 (%12)	

*: Chi-square

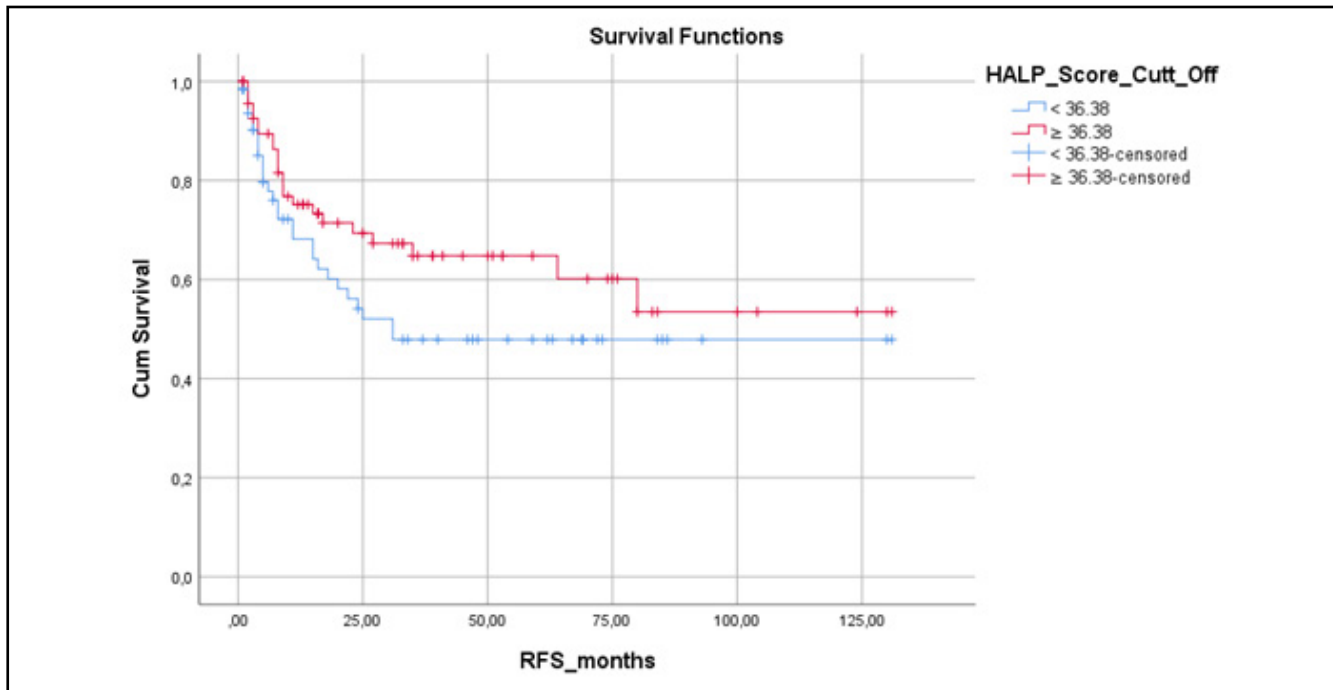


Figure 3. PFS Curve According to HALP Score (Kaplan-Meier Analysis)

Preoperative anemia is a marker of systemic health and it is a tumor burden. In this sense, it has been widely studied in the context of oncological outcomes. While our analysis did not reveal a significant relationship between preoperative anemia and recurrence, prior studies have reported conflicting results. Xia et al. identified a significant association between preoperative anemia and early recurrence in bladder and renal cancers, and Furrer et al. demonstrated increased progression risk in anemic patients requiring erythrocyte transfusions (5,12,13). These inconsistencies suggest that the impact of anemia on recurrence may be influenced by additional factors, such as treatment modalities or patient comorbidities, necessitating more nuanced exploration in future studies.

Low preoperative albumin levels, a reflection of nutritional and inflammatory status, have been consistently linked to adverse outcomes in multiple malignancies. Our findings corroborate this, as low albumin levels were significantly associated with increased postoperative recurrence risk ($p=0.032$). This observation is in line with previous research, such as Djalat et al.'s study in bladder cancer, Liu et al.'s work in gastric cancer and Miura et al.'s findings in non-small cell lung cancer (7,14,15). Collectively, these results

highlight hypoalbuminemia as a potential universal marker of poor oncological outcomes, reinforcing its importance in preoperative risk stratification.

The prognostic utility of the HALP score, a composite index incorporating hematological and biochemical parameters, has been demonstrated across various malignancies. In our study, a low HALP score was significantly associated with advanced pT stage but not with nodal involvement, suggesting its utility may be more reflective of local tumor aggressiveness rather than systemic disease spread. This observation aligns with findings in other malignancies. For instance, Ekici et al. found that in patients with testicular cancer, a low HALP score was significantly associated with advanced T, N, and M stages, emphasizing its potential as a marker of tumor progression (16). Similarly, Zhao et al. demonstrated that low HALP scores were strongly associated with advanced TNM stage in non-small cell lung cancer (17). Additionally, Zhang et al. reported that low HALP scores were associated with advanced lymph node positivity in tongue squamous cell carcinoma, although the association with advanced T stage was not statistically significant (18). However, variability exists, as evidenced by Zhang et al.'s study on lung adenocarcinoma, where a low HALP score did

not show a statistically significant association with advanced T stage or N stage (19). These discrepancies underscore the need for further disease-specific validation to clarify the prognostic implications of the HALP score across different cancer types.

The HALP score has emerged as a promising prognostic marker across various malignancies, with its association with recurrence and survival outcomes being increasingly recognized. In our study, a low HALP score was significantly associated with recurrence in patients with muscle-invasive bladder cancer, underscoring its potential as a marker of tumor aggressiveness. This finding is consistent with studies in other malignancies. For instance, in hepatocellular carcinoma, Liu et al. demonstrated that a low HALP score was a strong predictor of early recurrence following radical liver resection (20). Similarly, Zhao et al. found that a low HALP score was significantly associated with recurrence in non-small cell lung cancer while in lung adenocarcinoma, Zhang et al. reported that a low HALP score could predict recurrence risk (17,19). These results highlight the versatility of the HALP score as a prognostic indicator in different cancer types.

In gynecological malignancies, such as endometrial cancer, Wang et al. demonstrated that a low HALP score is an effective prognostic marker for recurrence (21). Additionally, reduced PFS has been reported in patients with malignancies such as gastrointestinal stromal tumors and cervical cancer, further emphasizing the significance of the HALP score in predicting oncological outcomes (22,23). Consistent with these findings, our study confirms the association of a low HALP score with recurrence and contributes to the growing body of evidence supporting its prognostic utility. Notably, this study is the first to evaluate the prognostic value of the HALP score in MIBC, marking an important contribution to literature and paving the way for its potential integration into clinical decision-making.

This study has certain limitations that should be acknowledged while also emphasizing its contributions to literature. The retrospective design, although practical for evaluating prognostic factors in a real-world setting, may limit the standardization of data collection and introduce potential selection bias. The sample size, while sufficient to

demonstrate statistically significant findings, may limit the statistical power of subgroup analyses and the generalizability of results. As a single-center study, the findings may not fully capture variations across diverse populations or healthcare systems. Nevertheless, the HALP score was rigorously evaluated as an independent prognostic marker, making this study a valuable foundation for future research. While the absence of combined analyses with other established prognostic factors and the lack of long-term follow-up data may limit the development of a comprehensive prognostic model, the significant associations identified in this study provide strong evidence for the potential clinical utility of the HALP score. Moreover, the influence of adjuvant or neoadjuvant therapies on the prognostic value of the HALP score warrants further investigation in larger, multicenter studies. Despite these limitations, this study represents an important step in exploring the prognostic role of the HALP score in MIBC, contributing novel and clinically relevant insights to the field.

CONCLUSION

Our study pointed out that the HALP score is a limited yet statistically significant prognostic marker for predicting progression in patients with MIBC. While the sensitivity and specificity values of the HALP score in predicting progression, based on the optimal cut-off point, were found to be moderate, these findings highlight its limitations as a standalone prognostic marker. Nonetheless, as one of the first studies to investigate the prognostic value of the HALP score in MIBC, our work makes a valuable contribution to the literature, suggesting that the HALP score should be considered in patient management. Future prospective studies with larger sample sizes are needed to evaluate the combination of the HALP score with other prognostic factors and its impact on long-term patient outcomes, ultimately supporting its potential use in the development of individualized treatment strategies.

Conflict of Interest: The authors declare that they have nothing to disclose.

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Ethical Approval: Our study was approved by the Scientific Research Ethics Committee of Haydarpaşa Numune Training and Research Hospital on December 17, 2024, with decision number HNEAH-GOAEK/KK/2024/159.

Author Contributions: Conception and Design; Kayar R. Data acquisition; Kayar K, Demir S. Data analysis and interpretation; Kayar K, Artuk I. Drafting the manuscript; Kayar R. Critical revision of the manuscript for scientific and factual content; Kayar R, Kayar K, Tokuc E. Statistical analysis; Kayar R, Kayar K. Supervision; Ozturk MI.

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