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HALP Score as a Predictor of Neoadjuvant Chemotherapy Response in Gastric and Gastroesophageal Junction Adenocarcinoma

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ABSTRACT

Objective: The hemoglobin, albumin, lymphocyte, and platelet (HALP) score reflects inflammation and nutrition and has predictive value in cancers. This study investigates the relationship between HALP score and neoadjuvant chemotherapy (NAC) response in resectable gastric adenocarcinoma (GA) and gastroesophageal junction (GEJ) adenocarcinomas.

Material and Methods: This retrospective, single-center study analyzed patients with resectable GEJ or GA undergoing NAC. Patients were grouped as treatment response positive (TR+) and treatment response negative (TR-). HALP scores, calculated prior to treatment, were categorized using a receiver operating characteristic (ROC)-derived cut-off, and their association with treatment response was evaluated.

Results: A total of 67 patients (median age 61, 73.1% male) were analyzed, with 36 (53.7%) showing TR+ and 31 (46.2%) showing TR-. ROC analysis revealed a significant association between HALP score and TR+ (area under the curve: 0.708, p=0.004). Older age [odds ratio (OR): 2.87, p=0.046], cN0-1 (OR: 3.43, p=0.023), and higher HALP score (OR: 5.55, p=0.001) were associated with a higher likelihood of TR+. Median progression-free survival (PFS) was 26.7 months [95% confidence interval (CI): 14.7-38.7], and median overall survival (OS) was 43.8 months (95% CI: 27.9-59.8) for the entire cohort. The high HALP group had improved PFS [27.1 months (95% CI: 12.1-41.9) vs. 23.6 months (95% CI: 4.6-42.7), p=0.120] and OS [38.4 months (95% CI: 18.2-58.5) vs. 43.8 months (95% CI: 17.9-69.8), p=0.270], although not statistically significant.

Conclusion: HALP score may serve as a predictive marker for NAC response in GEJ and GA, with potential implications for patient stratification.

Keywords: Neoadjuvant therapy; precision medicine; stomach neoplasms; tumor biomarker

INTRODUCTION

Gastric cancer is a highly prevalent and aggressive cancer worldwide.[1] Recent histological and anatomical classifications categorize gastroesophageal tumors into three main subtypes: Esophageal and gastroesophageal junction (GEJ) adenocarcinoma, gastric adenocarcinoma (GA), and esophageal squamous cell carcinoma.[2,3] These classifications reflect the current understanding of anatomy, histopathology, etiology, and molecular characteristics.

At diagnosis, a significant proportion of GEJ and GAs are locally advanced (LA). For resectable tumors that are T3 and/or node-positive, perioperative chemotherapy has become the standard treatment, addressing the risk of predominantly systemic disease recurrence.[4] While older regimens containing epirubicin or docetaxel with platinum and fluorouracil were previously common, the most significant recent development in the treatment of GEJ and GAs is the fluorouracil, leucovorin, oxaliplatin and docetaxel 4 (FLOT4) trial.[5-8] This phase 3 study evaluated the use of perioperative FLOT chemotherapy.

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The regimen was administered for four cycles before surgery and four cycles after. The trial demonstrated significantly better survival outcomes with the FLOT regimen compared to previous standard chemotherapy options, while maintaining a similar safety profile in both treatment arms.[7,8] As a result, FLOT has emerged as the standard treatment of choice for patients with LA GEJ and GA.[4,9] Despite these advances, a substantial group of patients with LA disease do not respond to neoadjuvant chemotherapy (NAC). As a result, ongoing research seeks reliable biomarkers to predict treatment response in this population.

GA frequently leads to malnutrition and weight loss, both of which have negative impacts on prognosis.[10] The progression and clinical outcomes are strongly influenced by both the systemic inflammation and the patient's nutritional condition. Various markers have been recognized for their predictive value in assessing prognosis.[11,12] Among them, the hemoglobin, albumin, lymphocyte, and platelet (HALP) score, which integrates both systemic and nutritional parameters, has been proposed as a prognostic indicator across multiple malignancies, including GA.[13-17] Low HALP scores have been linked to poor nutritional condition and unfavorable survival outcomes. However, the role of HALP score in predicting outcomes for patients with LA GEJ and GAs receiving NAC has not been well-defined.

The objective of this study is to investigate the potential of the HALP score as a predictor of pathological response, progression-free survival (PFS), and overall survival (OS) in patients with LA GEJ and GA who undergo NAC and subsequent radical surgery.

MATERIAL AND METHODS

The authors state that they have obtained Ankara University Clinical Research Ethics Committee approval (date: October 25, 2024, approval number: İ09-708-24) and have followed the principles outlined in the Declaration of Helsinki.

Patients

This retrospective study includes demographic and pathological data from patients with LA GEJ or GAs, treated with NAC at Ankara University Faculty of Medicine between June 2017 and February 2024. Eligible patients were aged 18 and above, with a confirmed diagnosis of GEJ or GA through endoscopic biopsy. Patients with cT3-4 and/or cNode-positive disease, as determined by endoscopic ultrasound, computed tomography (CT) or positron emission tomography-CT scans, were included, provided that patients with distant metastases or those who received perioperative radiotherapy were excluded.[18] In all cases, diagnostic laparoscopy was performed to rule out peritoneal metastases at initial staging. All patients had undergone D2 lymph node dissection. Data on patient demographics, chemotherapy regimens, pathological staging, microsatellite instability (MSI) status, and human epidermal growth factor receptor-2 (HER-2) amplification status were documented. HER-2 amplification was assessed using immunohistochemistry (IHC); cases with a +2 IHC score were further evaluated using *in situ* hybridization to confirm the HER-2 status. Patients with incomplete clinical data or follow-up, or those with clear signs of infection or autoimmune disease, were excluded from the study.

Radiological response after NAC was assessed using the RECIST 1.1 criteria, while pathological response evaluation followed the College of American Pathologists protocol.[19,20]

Patients were grouped according to their response to NAC. Treatment response positive (TR+) was defined as pathological complete, near-complete, or partial response in resected specimens, whereas treatment response negative (TR–) included patients with pathological non-response after resection, and those who did not undergo resection due to intraoperative detection of peritoneal metastases, considered clinical/radiological non-responders. Factors predicting treatment response were also evaluated.

PFS was defined as the time from the index date to recurrence. The index date was the start of adjuvant chemotherapy; for patients without adjuvant therapy, the date of surgery; and for those not undergoing surgery, the completion date of first-line chemotherapy.

Definition of HALP Score

The HALP score was assessed using hemogram and biochemical values obtained within one week prior to the start of NAC with the formula: hemoglobin (g/L) × albumin (g/L) × lymphocyte count (/L) ÷ platelet count (/L).[15] As no universally accepted cut-off value for the HALP score was available in the literature, a receiver operating characteristic (ROC) curve analysis was used to identify the most suitable threshold.

Statistical Analysis

SPSS version 25 was used for statistical analysis. Continuous variables were described as mean ± standard deviation or median (range). Categorical variables were reported as frequencies and percentages. Groups were compared using the appropriate statistical tests (t-test, Mann-Whitney U test, chi-square test, or Fisher's exact test). ROC curve analysis was applied to determine the optimal HALP score cut-off value, which was subsequently used to classify patients into low-HALP and high-HALP score groups. Kaplan-Meier analysis was used to determine survival outcomes, and survival curves were generated using R (version 4.5.1). Factors influencing pathological response and survival were assessed using binary logistic regression. A two-sided p-value of <0.05 was considered statistically significant.

RESULTS

A total of 67 patients, with a median age of 61 years (interquartile range: 32-77), 73.1% male, were included. The primary tumor was located in the GEJ in 20 patients (29.9%), in the proximal stomach in 34 patients (50.7%), and in the distal stomach in 13 patients (19.4%). According to the Lauren classification, 51 patients (76.1%) had intestinal-type adenocarcinoma, and 24 patients (35.8%) had signet-ring cell adenocarcinoma. Of the 47 patients whose HER-2 status was assessed, five (7.5%) had HER-2 amplification, and of the 34 patients whose MSI status was evaluated, two (3%) had MSI-high tumors. Clinically, 27 patients (40.2%) were cT4, and 42 (62.6%) had cN2-3 disease. Surgery was performed on 60 patients following neoadjuvant therapy, while 7 patients had surgery canceled due to the identification of peritoneal metastases during laparotomy, confirmed by frozen section pathology. These 7 patients were classified as non-responders to neoadjuvant therapy. Patients were grouped 36 patients (53.7%) in TR+ and 31 patients (46.2%) in the TR- group. The clinicopathological characteristics of both groups were similar, except for a higher proportion of cN2-3 patients in the TR- group (77.7% vs. 50%, p=0.025). The HALP score was higher in the TR+ group compared to the TR- group [20.70 (3.85-81.0) vs. 36.27 (1.86-74.91), p=0.004] (Table 1).

In both groups, the most commonly used regimen was FLOT both in the neoadjuvant (90.3% vs. 88.9%) and adjuvant (81% vs. 78.1%, p=0.504) setting. None of the patients received a >10% dose reduction in the neoadjuvant setting. Thus, treatment intensity was compared between groups based on duration and cycle number, with no significant differences

TABLE 1: Clinicopathological characteristic of patients.

	All patients, n=67		
	TR-, n=31	TR+, n=36	p-value
Age, years, median (IQR)	60 (32-75)	64 (40-77)	0.302
Gender, n (%)			
Male	22 (71)	27 (75)	0.786
Female	9 (29)	9 (25)	
ECOG performance status			
0	6 (19.4)	7 (19.4)	0.998
≥1	25 (80.6)	29 (80.6)	
Tumor location, n (%)			
GEJ	9 (20.9)	11 (30.6)	0.989
Proximal stomach	16 (51.6)	18 (50)	
Distal stomach	6 (19.4)	7 (19.4)	
Lauren classification, n (%)			
Intestinal type	24 (77.4)	29 (80.5)	0.767
Diffuse type	7 (22.6)	7 (19.4)	
Signet ring carcinoma, n (%)	11 (35.5)	13 (36.1)	1.000
Clinical T stage, n (%)			
cT3	18 (58.1)	22 (61.1)	0.809
cT4	13 (41.9)	14 (38.9)	
Clinical N stage, n (%)			
cN0-1	7 (22.6)	18 (50)	**0.025**
cN2-3	24 (77.7)	18 (50)	
MSI status, n (%)			
MSS	16 (94.1)	16 (94.1)	1.000
MSI-high	1 (5.9)	1 (5.9)	
HER-2 amplification, n (%)	2 (8.3)	3 (13.0)	0.666
HALP score, median (IQR)	20.70 (3.85-81.0)	36.27 (1.86-74.91)	**0.004**

ECOG: Eastern Cooperative Oncology Group; GEJ: Gastroesophageal junction; HALP: Hemoglobin, albumin, lymphocyte and platelet score; HER-2: Human epidermal growth factor receptor-2; IQR: Interquartile range; MSI: Microsatellite instability; MSS: Microsatellite stable; TR-: Treatment response negative; TR+: Treatment response positive.

observed between the group. Four patients in each group did not receive adjuvant chemotherapy due to postoperative complications or difficulty tolerating treatment (Table 2).

The cut-off value identified for HALP was 20.6866, with scores <20.6866 categorized as low-HALP and those ≥20.6866 as high-HALP. For this value, sensitivity and specificity were 86% and 51%. The ROC curve analysis demonstrated a significant relationship between the HALP score and pathological response, with an area under the curve of 0.708 [95% confidence interval (CI): 0.579-0.837], and a p-value of 0.004, indicating a statistically significant result (Figure 1). The clinicopathological characteristics were comparable between the low- and high-HALP groups (Supplementary Table 1). The rate of TR+ was significantly higher in the high-HALP group (67.4% vs. 23.8%, p=0.001).

Factors that may influence the response to NAC were analyzed. Older age (≥65 years) [odds ratio (OR): 2.87, 95% CI: 1.020-8.104, p=0.046], fewer than 3 lymph node metastases (cN0-1) at diagnosis (OR: 3.43, 95% CI: 1.181-9.952, p=0.023), and higher HALP score (OR: 5.55, 95% CI: 1.942-15.890, p=0.001) were significantly associated with an increased likelihood of achieving TR+. In the multivariate regression analysis, a high HALP score (OR: 6.97, 95% CI: 1.953-24.901, p=0.003) and cN0-1 at diagnosis [OR: 3.71 (95% CI: 1.092-12.646), p= 0.036] were found to be independent predictors of pathological response (Table 3).

Of the 60 patients who underwent surgery after neoadjuvant chemotherapy, 56 had positive cN status at the time of diagnosis. In the subgroup analysis of these 56 patients, 22 (39.3%) showed ypN0 and 34 (60.7%) showed ypN+. In the high-HALP group, the proportion of ypN0 patients was significantly higher (47.5% vs. 18.8%, p=0.047). Cox regression analysis indicated a borderline-significant association between high HALP score and pathological regression of

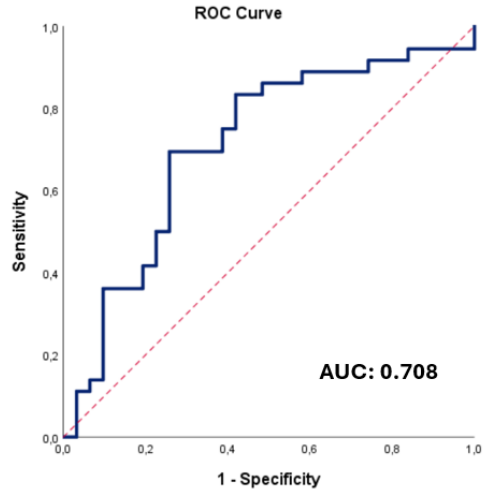

FIGURE 1: ROC curve of HALP score for pathological response.

ROC: Receiver operating characteristic; HALP: Hemoglobin, albumin, lymphocyte and platelet score; AUC: Area under the curve

TABLE 2: Treatment characteristics of patients.

	All patients, n=67		
	TR-, n=31	TR+, n=36	p-value
Neoadjuvant regimen			
FLOT	28 (90.3)	32 (88.9)	1.000
Other*	3 (9.7)	4 (11.1)	
Duration of NAC, cycles (median)	4 (3-7)	5 (3-7)	0.881
Radiological response evaluation, n (%)			
NA	3 (9.7)	4 (11.1)	
PR	7 (22.6)	25 (69.4)	**0.010**
SD	18 (58.1)	7 (19.4)	
PD	3 (9.7)	0 (0)	
Adjuvant chemotherapy, n (%)			
Received	21 (84)	32 (88.9)	0.810
Not received	4 (16)	4 (11.1)	
Adjuvant chemotherapy regimen, n (%)			
FLOT	17 (81)	25 (78.1)	0.504
Other**	4 (19.1)	7 (21.9)	

*In the TR- group, 1 received DCF, 2 received FOLFOX; in the TR+ group, 1 received DCF, 2 received FOLFOX. ** In the TR- group, 1 received DCF, 3 received FOLFOX; in the TR+ group, 1 received DCF, 4 received FOLFOX, and 2 received capecitabine monotherapy. DCF: Docetaxel, cisplatin, fluorouracil; FLOT: Fluorouracil, leucovorin, oxaliplatin and docetaxel; FOLFOX: Fluorouracil, leucovorin, oxaliplatin; IQR: Interquartile range; NAC: Neoadjuvant chemotherapy; TR-: Treatment response negative; TR+: Treatment response positive.

TABLE 3: Univariate and multivariate analysis of factors affecting treatment response.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (<65 vs. ≥65 years)	2.87 (1.020-8.104)	**0.046**	2.37 (0.737-7.672)	0.147
Gender (female vs. male)	1.22 (0.416-3.621	0.711		
Tumor location (proximal*vs. distal)	1.01 (0.299-3.388)	0.993		
Lauren classification (diffuse vs. intestinal type)	2.33 (0.167-32.584)	0.529		
Signet ring carcinoma	1.02 (0.377-2.799)	0.957		
Clinical T stage (cT3 vs. cT4)	1.13 (0.426-3.020)	0.800		
Clinical N stage (cN2-3 vs. cN0-1)	3.43 (1.181-9.952)	**0.023**	3.71 (1.092-12.646)	**0.036**
MSI status (MSS vs. MSI-high)	1.00 (0.057-17.411)	1.000		
HER-2 amplification	1.65 (0.250-10.910)	0.603		
HALP score (low vs. high)	6.61 (2.036-21.486)	**0.002**	6.97 (1.953-24.901)	**0.003**
NAC (FLOT vs. other)	1.16 (0.240-5.667)	0.848		

*Tumors located at the gastroesophageal junction and proximal stomach were grouped together. FLOT: Fluorouracil, leucovorin, oxaliplatin and docetaxel; HALP: Hemoglobin, albumin, lymphocyte and platelet score; HER-2: Human epidermal growth factor receptor-2; MSI: Microsatellite instability; MSS: Microsatellite stable; NAC: Neoadjuvant chemotherapy; CI: Confidence interval; OR: Odds ratio.

tumors in the lymph nodes [OR: 3.91 (95% CI: 0.966-15.905), p=0.056].

The cohort was followed for a median period of 22.8 months (95% CI: 3.2-86.5 months). During this period, median PFS was 26.7 months (95% CI: 14.7-38.7) and OS was 43.8 months (95% CI: 27.9-59.8). Although the group with a high HALP score showed slightly improved PFS [27.1 months (95% CI: 12.1-41.9) vs. 23.6 months (95% CI: 4.6-42.7), p=0.120], and OS 38.4 months (95% CI: 18.2-58.5) vs. 43.8 months (95% CI: 17.9-69.8), p=0.270], these differences did not reach statistical significance (Figure 2).

DISCUSSION

In this study, we showed that high HALP score and having less than three positive lymph nodes at diagnosis are predictive factors for response to NAC in patients with LA GEJ and GA who underwent surgery. Additionally, while not statistically significant, a higher HALP score was linked to better survival outcomes.

In the FLOT4-AIO trial, 55% of patients achieved a pathological response following neoadjuvant FLOT, with 16% achieving a complete pathological response.[8] In our study, the pathological response rate was 53.5%, consistent with the trial's results. However, no patients in our cohort achieved a complete pathological response. Several factors could explain the absence of complete responses in our study. First, our cohort's higher proportion of more aggressive or advanced tumors (e.g., cN2-3 disease in 62.6% of patients), may result in reduced chemosensitivity compared to the FLOT4 trial population. Moreover, biological differences, such as tumor heterogeneity or molecular subtypes, could play a role in diminished response rates. In our study, 35.8% of patients had signet ring cell carcinoma, which is known to be less responsive to chemotherapy.

Perioperative Durvalumab plus FLOT is now the standard of care for patients with PD-L1 CPS ≥1 LA GA and GEJ adenocarcinomas, according to recent guidelines.[4] The HALP score may also have predictive value in chemo-immunotherapy. Higher HALP scores are, in fact, linked to better survival outcomes, according to new data from cohorts treated with immune checkpoint inhibitors in various cancers.[21] To determine whether HALP can function similarly to a biomarker in perioperative chemo-immunotherapy for GEJ and GA, prospective validation is crucial.

Chronic inflammation is a key driver of tumor formation, influencing processes such as malignant transformation, proliferation, invasion, angiogenesis, and metastasis. It contributes to tumor progression and resistance to chemotherapy and radiotherapy.[22,23] Tumor oxygenation is largely determined by hemoglobin; hypoxia caused by anemia has been shown to increase resistance to radiotherapy and chemotherapy. Systemic inflammation and nutritional reserve are represented in albumin; hypoalbuminemia is associated with impaired drug metabolism and a reduced ability to tolerate cytotoxic treatment.[24] Low lymphocyte counts are associated with immune evasion and a suboptimal treatment response. Lymphocytes are essential for antitumor immune surveillance. By releasing pro-angiogenic factors and protecting circulating tumor cells from immune destruction, platelets contribute to the progression of tumors.[25] The HALP score offers a composite metric that reflects the interactions between the tumor and the host as well as the nutritional-inflammatory milieu of the host.[13,14,26] In our study, although

not statistically significant, we found that patients with low-HALP had worse survival, consistent with findings in the literature. Additionally, while HALP has been shown to predict treatment response in breast and rectal cancer patients receiving neoadjuvant therapy, similar research in LA GEJ and GA is lacking.[27-30] Our findings indicate a notable treatment response rate of 67% in the high HALP score group, with multivariate regression analysis suggesting that HALP score serves as an independent predictor of TR+.

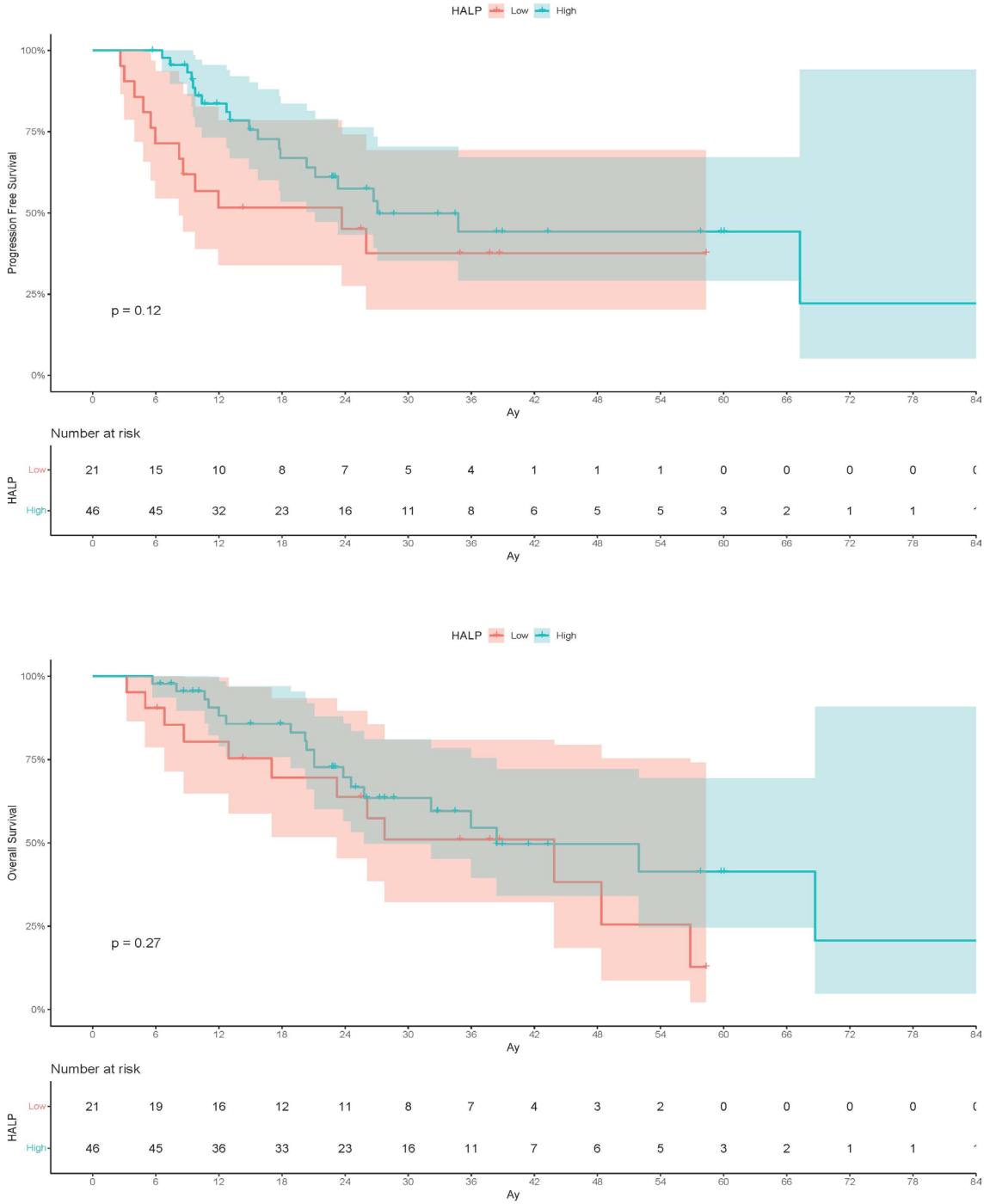

FIGURE 2. Kaplan-Meier analyses of patients according to HALP score: a) Progression-free survival and b) Overall survival.
HALP: Hemoglobin, albumin, lymphocyte and platelet score

By combining hematologic and nutritional parameters into a single composite index, the HALP score offers a more comprehensive view than other inflammatory or nutritional markers like neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, or prognostic nutritional index. HALP shows the complex link between host nutritional status and systemic inflammation rather than a single biological pathway. By providing a broader understanding of patient condition than traditional indicators, this integrative approach might help to explain why HALP demonstrated predictive ability for treatment response in our cohort.

Previous studies have shown that ypN0 status in GEJ and GA undergoing NAC is an independent prognostic factor indicating good survival.[31,32] Even though we found that patients with high HALP scores tended to have higher rates of nodal downstaging (ypN0), this association was not statistically significant and should be considered exploratory rather than conclusive.

Study Limitations

Nevertheless, our study has several limitations. There is a potential for selection bias because it is a retrospective analysis. Second, the generalizability of the findings to larger populations is constrained by the small sample size and short follow-up period. Furthermore, sarcopenia and other nutritional factors were not evaluated. The broad definition of TR+, which included complete, near-complete, and partial regression, is another limitation. This could have resulted in a higher overall response rate. These restrictions might have an impact on the validity of our findings. Therefore, larger prospective and multicenter studies are required to confirm the value and accuracy of the HALP score in predicting response to neoadjuvant chemotherapy.

CONCLUSION

Our study demonstrates that the HALP score serves as a promising predictive marker for pathological response to NAC in patients with LA GEJ and GA. The significant association between high HALP scores and improved pathological response highlights the potential of this biomarker in clinical practice. Identifying cost-effective, efficient pre-treatment indicators like the HALP score could help improve prognostic management and enhance postoperative care for this patient population. Further research involving larger, multicenter studies is essential to validate our findings and explore the integration of HALP scores into routine clinical assessment.

Ethics

Ethics Committee Approval: The authors state that they have obtained Ankara University Clinical Research Ethics Committee approval (date: October 25, 2024, approval number: İ09-708-24) and have followed the principles outlined in the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.B.K., E.B.K., G.U., H.A., P.K.T., Concept: B.B.K., E.B.K., G.U., H.A., P.K.T., Design: B.B.K., E.B.K., G.U., H.A., P.K.T., Data Collection or Processing: B.B.K., E.B.K., G.U., H.A., P.K.T., Analysis or Interpretation: B.B.K., E.B.K., G.U., H.A., P.K.T., Literature Search: B.B.K., E.B.K., G.U., H.A., P.K.T., Writing: B.B.K., E.B.K., G.U., H.A., P.K.T.

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SUPPLEMENTARY TABLE 1: Characteristics of the patients according to HALP grouping.			
	All patients, n=67		
	HALP-low (n=21)	HALP-high (n=46)	p-value
Age, years, median (IQR)	58 (32-74)	62 (39-77)	0.316
Gender, n (%)			
Male	17 (81)	32 (69.6)	0.388
Female	4 (19)	14 (30.4)	
ECOG performance status			
0	4 (19)	9 (19.6)	0.961
≥1	17 (81)	37 (80.4)	
Tumor location, n (%)			
GEJ-proximal stomach	16 (76.2)	38 (82.6)	0.526
Distal stomach	5 (23.8)	8 (17.4)	
Lauren classification, n (%)			
Intestinal type	18 (85.7)	33 (71.7)	0.384
Diffuse type	3 (14.3)	11 (23.9)	
Signet ring carcinoma, n (%)	9 (42.9)	15 (32.6)	0.426
Clinical T stage, n (%)			
cT3	13 (61.9)	27 (58.7)	0.805
cT4	8 (38.1)	19 (41.3)	
Clinical N stage, n (%)			
cN0-1	7 (33.3)	18 (39.1)	0.787
cN2-3	14 (66.7)	28 (60.9)	
MSI status, n (%)			
MSS	13 (92.9)	19 (95)	0.797
MSI-high	1 (7.1)	1 (5)	
HER-2 amplification, n (%)	1 (5.9)	4 (13.3)	0.640

ECOG: Eastern Cooperative Oncology Group; GEJ: Gastroesophageal junction; HALP: Hemoglobin, albumin, lymphocyte and platelet score; HER-2: Human epidermal growth factor receptor-2; IQR: Interquartile range; MSI: Microsatellite instability; MSS: Microsatellite stable.