

Research Article

Prognostic Significance of the Prognostic Nutritional Index and HALP Score in Patients with Metastatic Gastrointestinal Stromal Tumors: A Multicenter Retrospective Study

 Ali Aytaç,¹  Bilgin Demir,²  Mehmet Uzun,³  Onur Yazdan Balçık,⁴  Gökhan Çolak,²  İbrahim Karadağ,⁵  İlhan Öztop⁶

¹Department of Medical Oncology, University of Health Sciences, Mehmet Akif İnan Training and Research Hospital, Şanlıurfa, Türkiye
²Division of Medical Oncology, Department of Internal Medicine, Aydın Adnan Menderes University Faculty of Medicine, Aydın, Türkiye
³Department of Medical Oncology, University of Health Sciences, İzmir Tepecik Training and Research Hospital, İzmir, Türkiye
⁴Department of Medical Oncology, Alanya Alaaddin Keykubat University Hospital, Alanya, Türkiye
⁵Department of Medical Oncology, University of Health Sciences, Ankara Etlik City Hospital, Ankara, Türkiye
⁶Division of Medical Oncology, Department of Internal Medicine, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye

Abstract

Objectives: Gastrointestinal stromal tumors (GISTs) are rare mesenchymal neoplasms with variable prognosis, particularly in metastatic disease. The prognostic value of systemic nutritional and inflammatory indices, including the prognostic nutritional index (PNI) and hemoglobin, albumin, lymphocyte, and platelet (HALP) score, remains unclear.

Methods: This multicenter retrospective cohort study included 93 patients with metastatic GIST diagnosed between 2005 and 2023 across four oncology centers in Türkiye. Baseline PNI and HALP scores were calculated at metastatic diagnosis. Associations with progression-free survival (PFS) and overall survival (OS) were evaluated using Kaplan–Meier and Cox regression analyses.

Results: PNI and HALP were strongly correlated ($p < 0.001$). An independent association of PNI or HALP with PFS or OS was not demonstrated in multivariable analyses. Regional lymph node involvement and liver metastasis were independently associated with PFS, while regional lymph node involvement was independently associated with OS. PNI ≥ 40 was associated with longer OS in Kaplan–Meier analysis ($p = 0.046$), but not after adjustment.

Conclusion: An independent prognostic association of PNI or HALP with survival was not demonstrated in this cohort. Regional lymph node involvement was independently associated with PFS and OS, and liver metastasis with PFS.

Keywords: Gastrointestinal stromal tumor, HALP score, metastatic cancer, prognosis, prognostic nutritional index, systemic inflammation

Cite This Article: Aytaç A, Demir B, Uzun M, Balçık OY, Çolak G, Karadağ İ, Öztop İ. Prognostic Significance of the Prognostic Nutritional Index and HALP Score in Patients with Metastatic Gastrointestinal Stromal Tumors: A Multicenter Retrospective Study. EJMI 2026;10(4):559–570.

Address for correspondence: Ali Aytaç, MD. Department of Medical Oncology, University of Health Sciences, Mehmet Akif İnan Training and Research Hospital, Şanlıurfa, Türkiye

Phone: +90 506 914 10 24 **E-mail:** dr_aliaytac@hotmail.com

Submitted Date: August 29, 2026 **Revised Date:** September 15, 2026 **Accepted Date:** September 16, 2026

©Copyright 2026 by Eurasian Journal of Medical Investigation - Available online at www.ejmi.org

OPEN ACCESS This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.



Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal neoplasms found within the gastrointestinal (GI) tract, constituting about 1–2% of all primary malignancies in this system. Although their occurrence is relatively rare, GISTs are recognized as the most prevalent mesenchymal tumors, which are distinct from epithelial tumors, in the GI tract.^[1–3] These tumors originate primarily from the interstitial cells of Cajal or their precursor cells and usually manifest as subepithelial masses that develop from the layers of the bowel wall.^[1–5]

GISTs have the potential to arise anywhere along the GI tract, spanning from the esophagus down to the anus. The stomach is the predominant site of involvement, representing roughly 63% of diagnosed cases, followed by the small intestine—especially the jejunum and ileum—which accounts for nearly one-quarter of cases.^[6,7] Other less frequent primary locations include the duodenum (about 5%), colorectum (also approximately 5%), esophagus (less than or equal to 1%), and anus (under 0.5%).^[8] Occasionally, GISTs may develop in extragastrointestinal regions such as the omentum, mesentery, and peritoneum, although these occurrences are rare.^[1–5] The disease mainly affects older adults, with a median diagnosis age of 65 to 69 years, and occurs equally in males and females.^[9–11]

Approximately 20% of patients are diagnosed with metastatic disease initially. The liver, omentum, and peritoneum are the primary metastatic sites, with clinical symptoms including abdominal pain, gastrointestinal bleeding, or bowel obstruction. Prognosis in metastatic GIST depends on traditional clinicopathological factors such as tumor size, mitotic index, location, and rupture, as well as molecular features.^[7,12–15]

Molecularly, GISTs frequently harbor activating mutations in KIT (proto-oncogene receptor tyrosine kinase) and PDGFRA (platelet-derived growth factor receptor alpha) genes. Less commonly, mutations in the SDH (succinate dehydrogenase) gene family and other rare alterations occur.^[16–18] Mutation status critically influences response to tyrosine kinase inhibitors and clinical outcomes in metastatic cases. KIT exon 11 mutations correlate with better responses and prognosis, whereas KIT exon 9 and PDGFRA exon 18 D842V mutations are associated with poorer therapeutic response and survival.^[10,13–15]

Recently, host-related factors like systemic inflammation and nutritional status have gained attention as prognostic markers in cancer. Composite scores such as the hemoglobin, albumin, lymphocyte, and platelet (HALP) score and the prognostic nutritional index (PNI) serve as accessible indicators of immune–nutritional status and have shown prognostic relevance in various solid tumors.^[19–22] However,

their prognostic value in metastatic GIST remains unclear. This study therefore aims to evaluate the independent prognostic significance of HALP and PNI in metastatic GIST patients.

Materials and Methods

Study Design and Setting

This retrospective cohort study was conducted at four oncology centers in Türkiye. It included patients diagnosed with metastatic GISTs from January 2005 through December 2023. The study was approved by the Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee, which served as the central ethics committee (no: 334, date: 03.03.2023). This study was conducted in accordance with the principles of the Declaration of Helsinki. Patient data were collected exclusively from the participating centers. For all participating centers, institutional study permission was obtained from the hospital administration (Chief Physician's Office) prior to data collection. The requirement for informed consent was waived by the central ethics committee in accordance with national regulations, specifically the *Regulation on Clinical Trials of Drugs and Biological Products* issued by the Turkish Ministry of Health, due to the retrospective nature of the study and the use of anonymized patient data.

Participants

Participants were adults aged 18 years or older with histopathologically confirmed GIST and radiological evidence of metastatic disease either at diagnosis or during follow-up. Exclusion criteria were incomplete baseline laboratory data, presence of active infection or inflammatory conditions, hematological disorders, concurrent malignancies, or immunosuppressive treatment at diagnosis.

Data Sources and Variables

Demographic, clinical, and pathological information was systematically collected from the electronic medical records of the participating centers. The dataset encompassed variables such as patients' age, sex, primary tumor location, Eastern Cooperative Oncology Group (ECOG) performance status, sites of metastasis, systemic treatment regimens administered, and survival outcomes.

In addition, baseline laboratory parameters were recorded at the time of metastatic diagnosis, prior to the commencement of systemic therapy. These laboratory values included hemoglobin concentration, serum albumin levels, lymphocyte count, neutrophil count, and platelet count, providing essential biochemical and hematological profiles relevant to patient status and prognosis.

Assessment of PNI and HALP Scores

PNI was computed using the formula: $PNI = (10 \times \text{serum albumin [g/L]} + (0.005 \times \text{total lymphocyte count [}/\text{mm}^3])$. The HALP score was derived as follows: $HALP = (\text{hemoglobin [g/L]} \times \text{albumin [g/L]} \times \text{lymphocyte count [}/\text{L}]) \div \text{platelet count [}/\text{L}]$. Optimal cut-off points for both PNI and HALP scores were identified through receiver operating characteristic (ROC) curve analysis. However, no statistically significant cut-off values could be identified. Therefore, the cut-off values previously reported in the literature were adopted for the present analysis. The HALP score cut-off was defined according to the study by Acar et al.^[23], while the PNI cut-off was determined based on the study by Ishiyama et al.^[24]

Outcomes

Primary outcome was overall survival (OS), from metastatic diagnosis to death from any cause or last follow-up. Secondary outcome was progression-free survival (PFS), from first-line systemic therapy to radiological progression or death.

Statistical Analysis

Statistical analyses were performed using SPSS (v27.0). Categorical variables are presented as n (%), continuous variables as mean $\pm$ SD or median (range). Group comparisons used independent t-test or Mann–Whitney U test. Categorical associations were assessed with chi-square test. Survival curves were estimated by Kaplan–Meier (KM) and compared with log-rank test. Univariate Cox regression identified variables with $p < 0.10$ for inclusion in multivariable Cox regression analyses. In addition, PNI and HALP were included a priori in the multivariable models as the primary biomarkers of interest, irrespective of their statistical significance in univariate analyses. Results are shown as hazard ratios (HR) with 95% confidence intervals (CI). Significance was set at two-sided $p < 0.05$.

AI-assisted technologies: ChatGPT (OpenAI) was used solely for language editing and proofreading to improve the clarity and readability of the manuscript. The authors independently verified and approved all content and take full responsibility for the accuracy and integrity of the final manuscript. No AI-assisted technology was used for data collection, statistical analysis, interpretation of results, or generation of scientific content.

Results

Patient Characteristics

A total of 93 patients with metastatic GIST were included in the study. The median age was 57 years (range: 32–82 years), and 66.7% of the patients were male. The median

follow-up time for the study cohort was 73.3 months (95% CI: 57.5–89.1 months), as estimated using the reverse KM method. The most common primary tumor location was the small intestine, followed by the stomach. The baseline clinicopathological characteristics of the study population are summarized in Table 1.

Association Between PNI and HALP

According to the chi-square test, a statistically significant association was observed between HALP levels and PNI groups ($p < 0.001$). The proportion of patients with a HALP score ≥ 29 was markedly higher in the PNI ≥ 40 group (70.2%) compared with the PNI < 40 group, in which no patients had a HALP score ≥ 29 (Table 2).

No statistically significant associations were identified between PNI groups and sex, age at diagnosis, presence of comorbidities, or specific comorbid conditions. ECOG performance status, smoking status, tumor location, tumor size, mitotic index, lymph node involvement, metastatic sites (liver, peritoneum, non-regional lymph nodes, lung, pancreas, and spleen), first-line treatment dose, progression on first-line therapy, total number of treatment lines received, or death status (all $p > 0.05$; Table 2).

A statistically significant association was identified between PNI levels and HALP groups ($p < 0.001$). The proportion of patients with a PNI score ≥ 40 was substantially higher in the HALP ≥ 29 group (100.0%) compared with the HALP < 29 group (73.5%) (Table 3).

No statistically significant associations were observed between HALP groups and sex, age at diagnosis, presence of comorbidities, or specific comorbid conditions. ECOG performance status, smoking status, tumor location, tumor size, mitotic index, lymph node involvement, metastatic sites (liver, peritoneum, non-regional lymph nodes, lung, pancreas, and spleen), first-line treatment dose, progression on first-line therapy, total number of treatment lines received, or death status (all $p > 0.05$; Table 3).

Progression-Free Survival

When PFS durations were compared according to HALP levels, no statistically significant difference was observed ($p = 0.183$). The mean PFS was 60.4 months in patients with HALP < 29 and 98.9 months in those with HALP ≥ 29 . Although the mean PFS was numerically longer in the HALP ≥ 29 group, the KM survival curves and log-rank test results indicated that this difference was not statistically significant. These findings suggest that HALP alone does not have a decisive impact on PFS and that the two groups exhibit a similar PFS profile (Fig. 1).

No statistically significant difference was observed when PFS durations were compared according to PNI levels

Table 1. Baseline clinicopathological characteristics of the entire study population

Variable		Toplam (n=93)	
		n	%
Sex	Male	62	66.7
	Female	31	33.3
Age, years, median (range)	57 (32-82)		
Age at Diagnosis	<65	70	75.3
	≥65	23	24.7
Comorbidity	Absent	41	44.1
	Present	52	55.9
Comorbidities	Diabetes Mellitus	14	15.1
	Hypertension	37	39.8
	Coronary artery disease	6	6.5
	COPD	3	3.2
ECOG Performance Status	0	58	62.4
	1	28	30.1
	2	7	7.5
Smoking	No	57	61.3
	Yes	36	38.7
Tumor location	Stomach	37	39.8
	Small intestine	38	40.9
	Colon	12	12.9
	Rectum	3	3.2
	Liver	1	1.1
	Vagina	1	1.1
	Appendix	1	1.1
Tumor size	>2 ile ≤5 cm	17	18.3
	>5 ile ≤10 cm	40	43.0
	> 10 cm	36	38.7
Mitotic Index	≤5 mitoses/50HPFs	32	34.4
	>5 mitoses/50 HPFs	58	62.4
	Not available	3	3.2
Lymph Node Status	Absent	71	76.3
	Regional LN	22	23.7
Sites of Metastasis	Liver	45	48.4
	Peritoneum	12	12.9
	Non-regional LN	7	7.5
	Lung	5	5.4
	Pancreas	1	1.1
	Spleen	1	1.1

Table 1. Continued

Variable		Toplam (n=93)	
		n	%
First-line Treatment	Imatinib 400	82	88.2
	Imatinib 800	11	11.8
Progression on First-line Treatment	Absent	50	53.8
	Present	43	46.2
PNI	<40	9	9.7
	≥40	84	90.3
HALP	<29	34	36.6
	≥29	59	63.4

ECOG: Eastern Cooperative Oncology Group performance status; PNI: Prognostic Nutritional Index; HALP: Hemoglobin, albumin, lymphocyte, and platelet score.

($p=0.899$). The mean PFS was 34.5 months in patients with PNI <40 and 90.1 months in those with PNI ≥40. Although the mean PFS was numerically longer in the PNI ≥40 group, the KM survival curves and log-rank test results indicated that this difference was not statistically significant. These findings suggest that PNI alone does not have a decisive impact on PFS and that the two groups exhibit a similar PFS profile (Fig. 2).

In univariate Cox proportional hazards regression analysis, ECOG performance status of 2, presence of regional lymph node involvement, liver metastasis, non-regional lymph node metastasis, and the total number of treatment lines were significantly associated with PFS (Table 4). These factors were associated with an increased risk of disease progression.

In multivariate Cox regression analysis, regional lymph node involvement (HR=3.412, 95% CI: 1.567–7.427; $p=0.002$) and

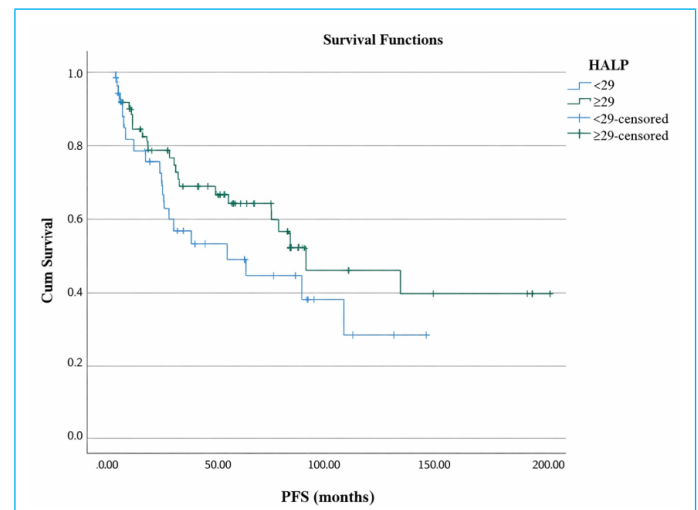
**Figure 1.** Progression-free survival according to HALP score.

Table 2. Demographic and clinical characteristics according to prognostic nutritional index (PNI)

Variable		PNI				p
		<40 (n=9)		≥40 (n=84)		
		n	%	n	%	
Sex	Male	6	66.7	56	66.7	1.000
	Female	3	33.3	28	33.3	
Age at Diagnosis	<65	5	55.6	65	77.4	0.218
	≥65	4	44.4	19	22.6	
Comorbidity	Absent	3	33.3	38	45.2	0.726
	Present	6	66.7	46	54.8	
Comorbidities	Diabetes Mellitus	1	11.1	13	15.5	1.000
	Hypertension	5	55.6	32	38.1	
	Coronary artery disease	0	0.0	6	7.1	
	COPD	0	0.0	3	3.6	
ECOG Performance Status	0	7	77.8	51	60.7	0.475
	1	2	22.2	26	31.0	
	2	0	0.0	7	8.3	
Smoking	No	5	55.6	52	61.9	1.000
	Yes	4	44.4	32	38.1	
Tumor location	Stomach	3	33.3	34	40.5	0.631
	Small intestine	4	44.4	34	40.5	
	Colon	1	11.1	11	13.1	
	Rectum	1	11.1	2	2.4	
	Liver	0	0.0	1	1.2	
	Vagina	0	0.0	1	1.2	
	Appendix	0	0.0	1	1.2	
Tumor size	>2 ile ≤5 cm	3	33.3	14	16.7	0.389
	>5 ile ≤10 cm	4	44.4	36	42.9	
	> 10 cm	2	22.2	34	40.5	
Mitotic Index	≤5 mitoses/50HPFs	2	22.2	30	35.7	0.241
	>5 mitoses/50 HPFs	6	66.7	52	61.9	
	Not available	1	11.1	2	2.4	
Lymph Node Status	Absent	6	66.7	65	77.4	0.437
	Regional LN	3	33.3	19	22.6	
Sites of Metastasis	Liver	3	33.3	42	50.0	0.488
	Peritoneum	1	11.1	11	13.1	1.000
	Non-regional LN	0	0.0	7	8.3	1.000
	Lung	1	11.1	4	4.8	0.406
	Pancreas	0	0.0	1	1.2	1.000
	Spleen	0	0.0	1	1.2	1.000
	First-line Treatment	Imatinib 400	7	77.8	75	89.3
Imatinib 800	2	22.2	9	10.7		

Table 2. Continued

Variable		PNI				p
		<40 (n=9)		≥40 (n=84)		
		n	%	n	%	
Progression on First-line Treatment	Absent	6	66.7	44	52.4	0.498
	Present	3	33.3	40	47.6	
Total Number of Treatments Received						
HALP Score	<29	9	100.0	25	29.8	<0.001*
	≥29	0	0.0	59	70.2	
Death	No	6	66.7	58	69.0	1.000
	Yes	3	33.3	26	31.0	

ECOG: Eastern Cooperative Oncology Group performance status; PNI: Prognostic Nutritional Index; HALP: Hemoglobin, albumin, lymphocyte, and platelet score. * $p < 0.05$ indicates a statistically significant association (Chi-square test).

Table 3. Demographic and clinical characteristics according to HALP score

Variable			HALP				p
			<29 (n=34)		≥29 (n=59)		
			n	%	n	%	
Sex	Male	24	70.6	38	64.4	0.703	
	Female	10	29.4	21	35.6		
Age at Diagnosis	<65	25	73.5	45	76.3	0.964	
	≥65	9	26.5	14	23.7		
Comorbidity	Yok	13	38.2	28	47.5	0.518	
	Var	21	61.8	31	52.5		
Comorbidities	Diabetes Mellitus	4	11.8	10	16.9	0.710	
	Hypertension	17	50.0	20	33.9	0.191	
	Coronary artery disease	1	2.9	5	8.5	0.410	
	COPD	0	0.0	3	5.1	0.297	
ECOG Performance Status	0	24	70.6	34	57.6	0.524	
	1	8	23.5	20	33.9		
	2	2	5.9	5	8.5		
Smoking	No	19	55.9	38	64.4	0.554	
	Yes	15	44.1	21	35.6		
Tumor location	Stomach	16	47.1	21	35.6	0.940	
	Small intestine	12	35.3	26	44.1		
	Colon	5	14.7	7	11.9		
	Rectum	1	2.9	2	3.4		
	Liver	0	0.0	1	1.7		
	Vagina	0	0.0	1	1.7		
	Appendix	0	0.0	1	1.7		
Tumor size	>2 ile ≤5 cm	4	11.8	13	22.0	0.324	
	>5 ile ≤10 cm	14	41.2	26	44.1		
	> 10 cm	16	47.1	20	33.9		

Table 3. Continued

Variable		HALP				p
		<29 (n=34)		≥29 (n=59)		
		n	%	n	%	
Mitotic Index	≤5 mitosis/50HPFs	13	38.2	19	32.2	0.374
	>5 mitosis/50 HPFs	19	55.9	39	66.1	
	Not available	2	5.9	1	1.7	
Lymph Node Status	Absent	24	70.6	47	79.7	0.460
	Regional LN	10	29.4	12	20.3	
Sites of Metastasis	Liver	15	44.1	30	50.8	0.682
	Peritoneum	3	8.8	9	15.3	0.525
	Non-regional LN	2	5.9	5	8.5	1.000
	Lung	1	2.9	4	6.8	0.649
	Pancreas	1	2.9	0	0.0	0.366
	Spleen	1	2.9	0	0.0	0.366
First-line Treatment	Imatinib 400	29	85.3	53	89.8	0.523
	Imatinib 800	5	14.7	6	10.2	
Progression on First-line Treatment	Absent	15	44.1	35	59.3	0.230
	Present	19	55.9	24	40.7	
Total Number of Treatments Received						
PNI	<40	9	26.5	0	0.0	<0.001*
	≥40	25	73.5	59	100.0	
Death	No	22	64.7	42	71.2	0.676
	Yes	12	35.3	17	28.8	

ECOG: Eastern Cooperative Oncology Group performance status; PNI: Prognostic Nutritional Index; HALP: Hemoglobin, albumin, lymphocyte, and platelet score.

* $p < 0.05$ indicates a statistically significant association (Chi-square test).

liver metastasis (HR=2.298, 95% CI: 1.066–4.951; $p=0.034$) remained independently associated with an increased risk of disease progression. Non-regional lymph node metastasis, ECOG performance status, PNI, and HALP did not retain statistical significance in the multivariate analysis (Table 4).

Overall Survival

No statistically significant difference was observed in the OS according to HALP levels ($p=0.567$). The mean OS was 90.3 months in patients with HALP <29 and 119.5 months in those with HALP ≥29. Although patients with a lower HALP score (<29) exhibited a shorter OS, this difference did not reach statistical significance. While the decline of the survival curve was slower and the mean OS was higher in the HALP ≥29 group, this difference should be interpreted with caution, as it may be attributable to chance. These findings suggest that, although the HALP score may have potential prognostic value, it does not demonstrate a statistically robust association with OS in this cohort (Fig. 3).

A statistically significant difference was compared according to PNI levels ($p=0.046$). The mean OS was 44.6 months

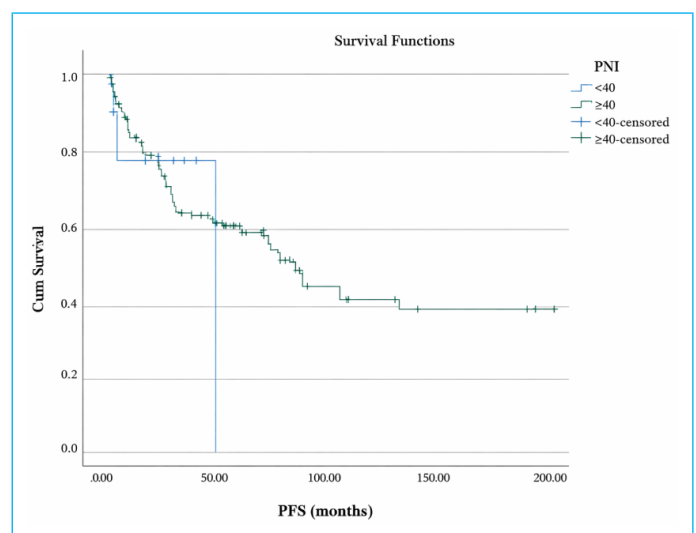


Figure 2. Progression-free survival according to PNI.

Table 4. Univariate and multivariate Cox proportional hazards analysis for progression-free survival

Variables	Univariate Analysis					Multivariate Analysis				
	B	sh	p	HR	95% CI HR	B	sh	p	HR	95% CI HR
Sex(Male)	0.060	0.327	0.855	1.061	0.559-2.014	x	x	x	x	x
Age at Diagnosis(≥65)	0.095	0.364	0.794	1.100	0.539-2.242	x	x	x	x	x
Comorbidity	0.344	0.321	0.283	1.411	0.752-2.647	x	x	x	x	x
Diabetes Mellitus	0.614	0.526	0.243	0.541	0.193-1.517	x	x	x	x	x
Hypertension	0.386	0.306	0.207	1.471	0.808-2.68	x	x	x	x	x
Coronary artery disease	0.648	0.480	0.177	1.911	0.746-4.894	x	x	x	x	x
COPD	0.553	0.603	0.359	1.738	0.533-5.668	x	x	x	x	x
ECOG Performance Status			0.089	-	-	-	-	0.127	-	-
1	0.382	0.333	0.251	1.465	0.763-2.815	0.644	0.384	0.094	1.903	0.896-4.042
2	0.994	0.465	0.033	2.701	1.085-6.723	1.100	0.689	0.110	3.004	0.779-11.586
Smoking	-0.113	0.313	0.717	0.893	0.484-1.648	x	x	x	x	x
Tumor size			0.304		-	x	x	x	x	x
>5 ile ≤10 cm	-0.398	0.422	0.346	0.672	0.294-1.537	x	x	x	x	x
> 10 cm	0.128	0.405	0.753	1.136	0.514-2.513	x	x	x	x	x
Mitotic Index(>5 mitosis/50 HPFs)	-0.129	0.321	0.687	0.879	0.468-1.648	x	x	x	x	x
Regional Lymph Node	0.883	0.323	0.006*	2.418	1.284-4.555	-1.227	0.397	0.002*	3.412	1.567-7.427
Site of Metastasis – Liver	1.330	0.350	<0.001*	3.782	1.903-7.515	0.832	0.392	0.034*	2.298	1.066-4.951
Site of Metastasis - Peritoneum	0.358	0.448	0.425	1.430	0.594-3.445	x	x	x	x	x
Site of Metastasis - Non Regional LN	1.043	0.488	0.033*	2.837	1.09-7.386	1.056	0.575	0.066	2.875	0.931-8.875
First-line Treatment (Imatinib 400 mg)	0.474	0.485	0.329	1.607	0.621-4.159	x	x	x	x	x
PNI(≥40)	0.077	0.606	0.899	1.080	0.329-3.54	-0.162	0.543	0.765	0.850	0.293-2.465
HALP(≥29)	0.408	0.308	0.166	1.503	0.821-2.751	-0.224	0.418	0.592	0.799	0.353-1.813

ECOG: Eastern Cooperative Oncology Group performance status; PNI: Prognostic Nutritional Index; HALP: Hemoglobin, albumin, lymphocyte, and platelet score. * In Cox proportional hazards regression analysis, a statistically significant association was observed (p<0.05)

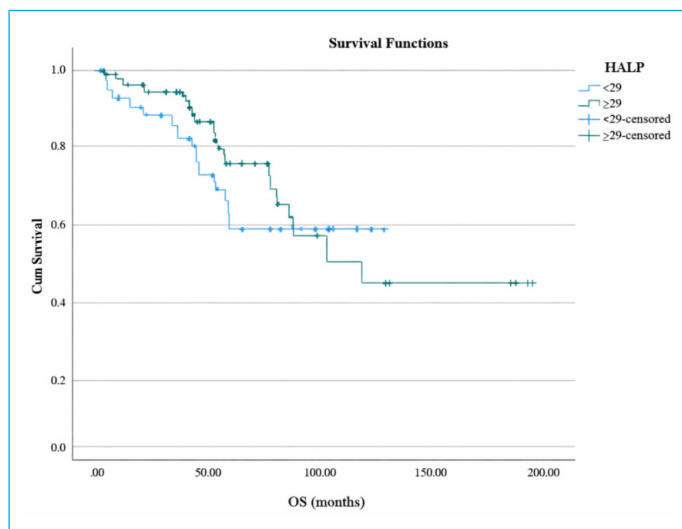


Figure 3. Overall survival according to HALP score.

in patients with PNI <40 and 124.3 months in those with PNI ≥40. Patients with a low PNI score (<40) had a significantly shorter OS. In the PNI ≥40 group, both the mean survival duration was longer and the decline in the survival curve was more gradual. These findings suggest that patients with better nutritional status and greater immunological reserve have a more favorable course during treatment (Fig. 4).

In univariate Cox proportional hazards regression analysis, regional lymph node involvement and liver metastasis were significantly associated with OS (Table 5). Both variables were associated with an increased risk of mortality.

In multivariate Cox regression analysis, regional lymph node involvement remained independently associated with an increased risk of mortality (HR=3.081, 95% CI: 1.324–7.167; $p=0.009$). Liver metastasis did not retain statistical signif-

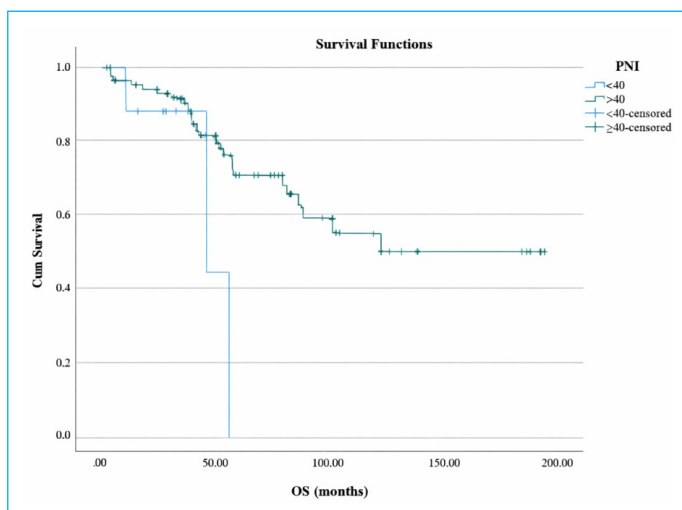


Figure 4. Overall survival according to PNI.

icance after adjustment (HR=1.616, 95% CI: 0.679–3.848; $p=0.278$). Neither PNI (HR=0.347, 95% CI: 0.102–1.181; $p=0.090$) nor HALP (HR=1.336, 95% CI: 0.478–3.737; $p=0.581$) was independently associated with OS (Table 5).

Discussion

In this multicenter retrospective study, we evaluated the prognostic value of PNI and HALP in patients with metastatic GISTs. While a significant correlation was identified between PNI and HALP scores, highlighting their common biological foundation related to systemic inflammation and nutritional status, an independent association of PNI or HALP with PFS or OS was not demonstrated in multivariable analyses. Instead, regional lymph node involvement and liver metastasis were independently associated with PFS, while regional lymph node involvement was the only independent prognostic factor for OS.

Inflammation- and nutrition-based indices such as PNI and HALP have been widely explored as prognostic biomarkers across a variety of solid tumors. Early studies, including that by Sagawa et al.^[25], highlighted the clinical relevance of Onodera's PNI in GI cancers, while Ishiyama et al.^[24] further demonstrated its independent prognostic value in advanced GI malignancies. Similarly, accumulating evidence supports the prognostic role of HALP. A recent systematic review and meta-analysis by Cai et al.^[19] showed that low HALP scores were consistently associated with unfavorable survival outcomes across multiple cancer types. In addition, studies by Demir et al.^[26] in advanced pancreatic cancer and Sargin and Düşünceli^[27] in gastric adenocarcinoma reported that low HALP scores were significantly associated with poorer survival, reinforcing the relevance of HALP as an integrated marker of hematologic and nutritional status in GI malignancies.

In contrast to these findings, our study did not identify an independent association between baseline PNI or HALP scores and survival outcomes in metastatic GIST after adjustment for clinically relevant covariates. This discrepancy may be explained by tumor-specific biological characteristics and the distinct therapeutic landscape of GIST. Unlike many epithelial malignancies, GIST is a molecularly driven tumor, and outcomes in the metastatic setting are largely influenced by targeted therapies and treatment sequencing rather than baseline inflammatory or nutritional status alone.

Importantly, regional lymph node involvement emerged as an independent prognostic factor for both PFS and OS in our cohort, while liver metastasis was independently associated with PFS but not OS. These findings suggest that the extent and distribution of metastatic disease may have

Table 5. Univariate and multivariate Cox proportional hazards analysis for overall survival

Variables	Univariate Analysis					Multivariate Analysis				
	B	sh	p	HR	95% CI HR	B	sh	p	HR	95% CI HR
Sex(Male)	0.502	0.435	0.249	1.652	0.704-3.879	x	x	x	x	x
Age at Diagnosis(≥65)	0.635	0.425	0.135	1.887	0.82-4.342	x	x	x	x	x
Comorbidity	0.347	0.392	0.376	1.415	0.656-3.052	x	x	x	x	x
Diabetes Mellitus	-0.753	0.734	0.305	0.471	0.112-1.985	x	x	x	x	x
Hypertension	0.393	0.373	0.292	1.482	0.713-3.078	x	x	x	x	x
Coronary artery disease	0.323	0.611	0.596	1.382	0.418-4.572	x	x	x	x	x
COPD	0.287	0.735	0.696	1.332	0.316-5.624	x	x	x	x	x
ECOG Performance Status			0.296		-	x	x	x	x	x
1	0.407	0.404	0.315	1.502	0.68-3.317	x	x	x	x	x
2	0.825	0.571	0.148	2.281	0.745-6.981	x	x	x	x	x
Smoking	0.183	0.377	0.628	1.201	0.573-2.517	x	x	x	x	x
Tumor size			0.565		-	x	x	x	x	x
>5 ile ≤10 cm	-0.502	0.511	0.326	0.605	0.222-1.648	x	x	x	x	x
> 10 cm	-0.166	0.502	0.740	0.847	0.316-2.265	x	x	x	x	x
Mitotic Index(>5 mitosis/50 HPFs)	0.332	0.405	0.412	1.394	0.63-3.084	x	x	x	x	x
Regional Lymph Node	1.136	0.377	0.003*	3.114	1.488-6.517	1.125	0.431	0.009*	3.081	1.324–7.167
Site of Metastasis – Liver	1.117	0.434	0.010*	3.055	1.304-7.155	0.480	0.443	0.278	1.616	0.679–3.848
Site of Metastasis - Peritoneum	0.584	0.547	0.286	1.793	0.614-5.24	x	x	x	x	x
Site of Metastasis - Non Regional LN	1.189	0.796	0.135	3.284	0.69-15.629	x	x	x	x	x
First-line Treatment (Imatinib 400 mg)	0.276	0.545	0.613	1.317	0.452-3.835	x	x	x	x	x
PNI(≥40)	1.204	0.638	0.059	3.332	0.954-11.643	-1.059	0.625	0.090	0.347	0.102–1.181
HALP(≥29)	0.216	0.377	0.568	1.241	0.592-2.6	0.290	0.525	0.581	1.336	0.478–3.737

ECOG: Eastern Cooperative Oncology Group performance status; PNI: Prognostic Nutritional Index; HALP: Hemoglobin, albumin, lymphocyte, and platelet score. * In Cox proportional hazards regression analysis, a statistically significant association was observed (p<0.05)

greater prognostic relevance than baseline inflammatory and nutritional indices in patients with metastatic GIST. Although PNI and HALP reflect nutritional and inflammatory status at baseline, their prognostic contribution may be less evident after adjustment for disease-related clinical factors. Therefore, these indices should be interpreted in conjunction with other clinical and disease-related characteristics rather than as standalone prognostic markers.

Several limitations of this study should be acknowledged when interpreting the findings. First, the retrospective design inherently relied on information that had already been recorded in routine clinical practice. Consequently, the study may be subject to selection bias, while the availability and completeness of clinical information may have limited the extent to which all relevant confounding factors could be accounted for in the analyses. Second, although

the study incorporated patients from multiple centers, differences among institutions in treatment approaches, clinical decision-making, and follow-up strategies may have introduced a degree of heterogeneity into the collected data. Such variations could have influenced the observed outcomes and may affect the extent to which our findings can be generalized to other clinical settings. Third, molecular characterization was not uniformly available for all patients. In particular, information regarding KIT, PDGFRA, and SDH mutation status was incomplete in a subset of the cohort. The absence of these molecular data prevented their systematic incorporation into the prognostic analyses and may have reduced the precision of risk assessment. Finally, PNI and HALP were derived exclusively from laboratory measurements obtained at the time of metastatic diagnosis. Since these parameters were not repeatedly evaluated

throughout the treatment course, potential changes in nutritional and inflammatory status over time could not be captured. Longitudinal assessment of these biomarkers might therefore provide additional information regarding their prognostic relevance during disease progression and treatment.

Conclusion

Although HALP and PNI are closely interconnected and both reflect systemic nutritional and inflammatory status in patients with metastatic GISTs, an independent prognostic association of these biomarkers with PFS or OS was not demonstrated in this cohort. Regional lymph node involvement was independently associated with both PFS and OS, while liver metastasis was independently associated with PFS. These findings suggest that disease-related clinical characteristics may have greater prognostic relevance than baseline nutritional and inflammatory indices in the metastatic setting. Although HALP and PNI are accessible and cost-effective markers of baseline nutritional and inflammatory status, their potential role as standalone prognostic markers requires further validation. Future prospective investigations should focus on longitudinal changes in nutritional and inflammatory markers combined with comprehensive molecular profiling to better define their prognostic role in patients with metastatic GISTs.

Disclosures

Ethics Committee Approval: The study was approved by the Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (no: 334, date: 03.03.2023).

Informed Consent: Informed consent was waived by the central ethics committee in accordance with national regulations, specifically the *Regulation on Clinical Trials of Drugs and Biological Products* issued by the Turkish Ministry of Health, due to the retrospective nature of the study and the use of anonymized patient data.

Conflicts of Interest: The authors declared that they have no competing interests.

Funding: The authors declared that this study did not receive any specific funding from the public, commercial, or not-for-profit funding agencies.

Use of AI for Writing Assistance: The authors declared that ChatGPT (OpenAI) was used solely for language editing and proofreading to improve the clarity and readability of the manuscript. The authors independently verified and approved all content and take full responsibility for the accuracy and integrity of the final manuscript. No AI-assisted technology was used for data collection, statistical analysis, interpretation of results, or generation of scientific content.

Authorship Contributions: Concept – AA, BD, MU, OYB, GÇ, İK, İÖ; Design – AA, BD, MU, OYB, GÇ, İK, İÖ; Supervision – AA, BD;

Data Collection or Processing: AA, BD, MU, OYB, GÇ, İK; Analysis or Interpretation: AA, BD, MU, OYB, GÇ, İK, İÖ; Literature Search: AA, BD, OYB; Writing: AA, BD, MU, OYB, GÇ, İK, İÖ; Critical Review: AA, BD, MU, OYB, GÇ, İK, İÖ.

Peer-review: Externally peer-reviewed.

References

1. Rubin BP, Fletcher JA, Fletcher CD. Molecular insights into the histogenesis and pathogenesis of gastrointestinal stromal tumors. *Int J Surg Pathol* 2000;8(1):5–10. [\[CrossRef\]](#)
2. Miettinen M, Lasota J. Gastrointestinal stromal tumors--definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch* 2001;438(1):1–12. [\[CrossRef\]](#)
3. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. *Hum Pathol* 1999;30(10):1213–20. [\[CrossRef\]](#)
4. Reith JD, Goldblum JR, Lyles RH, Weiss SW. Extragastrintestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome. *Mod Pathol* 2000;13(5):577–85. [\[CrossRef\]](#)
5. Medeiros F, Corless CL, Duensing A, Hornick JL, Oliveira AM, Heinrich MC, et al. KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. *Am J Surg Pathol* 2004;28(7):889–94. [\[CrossRef\]](#)
6. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg* 2000;231(1):51–8. [\[CrossRef\]](#)
7. Emory TS, Sobin LH, Lukes L, Lee DH, O'Leary TJ. Prognosis of gastrointestinal smooth-muscle (stromal) tumors: dependence on anatomic site. *Am J Surg Pathol* 1999;23(1):82–7. [\[CrossRef\]](#)
8. Singhal S, Singhal A, Tugnait R, Varghese V, Tiwari B, Arora PK, et al. Anorectal gastrointestinal stromal tumor: a case report and literature review. *Case Rep Gastrointest Med* 2013;2013:934875. [\[CrossRef\]](#)
9. Søreide K, Sandvik OM, Søreide JA, Giljaca V, Jureckova A, Bulusu VR. Global epidemiology of gastrointestinal stromal tumours (GIST): A systematic review of population-based cohort studies. *Cancer Epidemiol* 2016;40:39–46. [\[CrossRef\]](#)
10. Ma GL, Murphy JD, Martinez ME, Sicklick JK. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. *Cancer Epidemiol Biomarkers Prev* 2015;24(1):298–302. [\[CrossRef\]](#)
11. Cassier PA, Ducimetière F, Lurkin A, Ranchère-Vince D, Scoazec JY, Bringuier PP, et al. A prospective epidemiological study of new incident GISTs during two consecutive years in Rhône Alpes region: incidence and molecular distribution of GIST in a European region. *Br J Cancer* 2010;103(2):165–70. [\[CrossRef\]](#)

12. Khan J, Ullah A, Waheed A, Karki NR, Adhikari N, Vemavara-pu L, et al. Gastrointestinal stromal tumors (GIST): A population-based study using the SEER database, including management and recent advances in targeted therapy. *Cancers (Basel)* 2022;14(15):3689. [\[CrossRef\]](#)
13. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol* 2006;23(2):70–83. [\[CrossRef\]](#)
14. Taniguchi M, Nishida T, Hirota S, Isozaki K, Ito T, Nomura T, et al. Effect of c-kit mutation on prognosis of gastrointestinal stromal tumors. *Cancer Res* 1999;59(17):4297–300.
15. Bachet JB, Hostein I, Le Cesne A, Brahimi S, Beauchet A, Tabone-Eglinger S, et al. Prognosis and predictive value of KIT exon 11 deletion in GISTs. *Br J Cancer* 2009;101(1):7–11. [\[CrossRef\]](#)
16. Lasota J, Miettinen M. KIT and PDGFRA mutations in gastrointestinal stromal tumors (GISTs). *Semin Diagn Pathol* 2006;23(2):91–102. [\[CrossRef\]](#)
17. Celestino R, Lima J, Faustino A, Vinagre J, Máximo V, Gouveia A, et al. Molecular alterations and expression of succinate dehydrogenase complex in wild-type KIT/PDGFRA/BRAF gastrointestinal stromal tumors. *Eur J Hum Genet* 2013;21(5):503–10. [\[CrossRef\]](#)
18. Boikos SA, Stratakis CA. The genetic landscape of gastrointestinal stromal tumor lacking KIT and PDGFRA mutations. *Endocrine* 2014;47(2):401–8. [\[CrossRef\]](#)
19. Cai J, Wang B, Jing N, Zhang Y. Prognostic value of the HALP score in breast cancer: a systematic review and meta-analysis. *Front Oncol* 2025;15:1684940. [\[CrossRef\]](#)
20. Wang J, Jiang P, Huang Y, Tu Y, Zhou Q, Li N, et al. Prognostic value of the cutoffs for HALP in endometrial cancer. *Am J Clin Oncol* 2023;46(3):107–13. [\[CrossRef\]](#)
21. Zhao Y, Wang M, Zhang L, Li F, Yu H, Zhang Z, et al. Correlation analysis between serum cancer biomarkers and nutrition index score in lung cancer patients. *J Biomed Nanotechnol* 2024;20:276–82. [\[CrossRef\]](#)
22. Yamamoto M, Omori T, Masuike Y, Shinno N, Hara H, Sugase T, et al. Postoperative prognostic nutritional index as a useful prognostic factor in patients with gastric cancer. *Ann Gastroenterol Surg* 2025;9(6):1181–90. [\[CrossRef\]](#)
23. 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):1405–9. [\[CrossRef\]](#)
24. Ishiyama Y, Kondo T, Nemoto Y, Kobari Y, Ishihara H, Tachibana HHoshino I, Akutsu Y, et al. Predictive impact of prognostic nutritional index on pembrolizumab for metastatic urothelial carcinoma resistant to platinum-based chemotherapyPrognostic significance of the prognostic nutritional index in patients with advanced gastrointestinal cancer. *Anticancer Res.* 2021;41(3):1607–14. doi: 10.21873/anticancer-res.14909 [\[CrossRef\]](#)
25. Sagawa M, Katsube T, Konno S, Murayama M, Yamaguchi K, Isohata N, et al. The significance of Onodera's prognostic nutritional index for the treatment of gastrointestinal cancer. [Article in Japanese]. *Gan To Kagaku Ryoho* 2008;35(12):2253–5.
26. Demir N, Gökmen İ, Sağdıç Karateke Y, İlhan A, Yıldız F, Bayır Garbioğlu D, et al. HALP score as a prognostic marker for overall survival in advanced pancreatic cancer. *Front Oncol* 2025;15:1542463. [\[CrossRef\]](#)
27. Sargin ZG, Dusunceli I. The effect of HALP score on the prognosis of gastric adenocarcinoma. *J Coll Physicians Surg Pak* 2022;32(9):1154–9. [\[CrossRef\]](#)