ORIGINAL ARTICLE

DOI: 10.37047/jos.galenos.2025.2024.106668
J Oncol Sci 2025;11(1):14-21

Prognostic Significance of Inflammatory and Nutritional Biomarkers in Patients with Metastatic Gastric Cancer

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ABSTRACT

Objective: Metastatic gastric cancer (mGC) is an incurable disease and a leading cause of cancer-related deaths worldwide. The prognostic significance of systemic inflammation and nutritional scores in patients with mGC has been investigated; however, optimal biomarkers for prognosis need to be identified.

Material and Methods: This single-center retrospective study included patients with synchronous or metachronous mGC. We evaluated the associations between overall survival (OS) and Eastern Cooperative Oncology Group performance status (ECOG PS), serum albumin level, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, C-reactive protein-to-albumin ratio (CAR), prognostic nutritional index, modified Glasgow prognostic score (mGPS), and inflammatory burden index.

Results: In total, 203 patients were included, with 144 (71%) males and 59 (29%) females. The median age was 59 years (range: 21-82). The median follow-up time was 13.9 months (range: 2.7-114.9 months). Univariate analysis revealed that the ECOG PS (p=0.001), body mass index (BMI) (p=0.006), serum albumin level (p=0.002), CAR (p=0.013), and mGPS (p<0.001) were significant prognostic factors for OS. In the multivariate analysis, ECOG PS ≥1 vs. 0 [hazard ratio (HR): 1.5, 95% confidence interval (CI): 1.07-2.48; p=0.018], BMI <23.20 kg/m^2 vs. ≥23.20 kg/m^2 (HR: 0.70, 95% CI: 0.53-0.98; p=0.037) and mGPS 2 vs. 0-1 (HR: 1.3, 95% CI: 1.1-1.7; p=0.001) were independent predictors of poorer OS.

Conclusion: Our findings suggested that pretreatment BMI and the mGPS may be significant prognostic biomarkers for predicting OS in patients with mGC. A low BMI and high mGPS are associated with poor survival outcomes.

Keywords: Stomach neoplasms; body mass index; nutritional status; inflammation; survival

INTRODUCTION

Gastric cancer (GC) is one of the most prevalent causes of cancer-associated mortality, with about 1 million new cases reported annually. In 2022, about 659,853 deaths occurred due to GC; its incidence and mortality rank 5th in the world.[1] GC frequently manifests as an advanced, unresectable, or metastatic disease. Advanced-stage GC is often incurable, and the main goals of systemic treatment are symptom palliation, enhancing the quality of life, and prolonging survival. Despite the median overall survival (OS) approaching about 20 months with the addition of immunotherapy and monoclonal antibodies to fluoropyrimidine and platinum-based conventional chemotherapy, the prognosis for advanced GC patients remains unfavorable.[2-4]

Cancer-associated inflammation and malnutrition are prevalent in patients with malignancies and significantly influence the progression and prognosis of tumors.[5,6] Immunologic factors affect the sensitivity of chemotherapy and may include tumor differentiation and the expression of particular genes.[7,8] Nutritional status during treatment also significantly influences the response to chemotherapy. However, accurate markers for estimating cancer response and patient prognosis before chemotherapy need to be identified for the optimal formulation of treatment strategies.

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Received: 07.11.2024 **Accepted:** 19.01.2025 **Publication Date:** 29.04.2025

Cite this article as: Guliyev M, Alan Ö, Safarov S, et al. Prognostic significance of inflammatory and nutritional biomarkers in patients with metastatic gastric cancer. J Oncol Sci. 2025;11(1):14-21

Available at www.jos.galenos.com.tr

Several studies have reported a robust link between the incidence and progression of GC and the tumor-inflammatory microenvironment.[8,9] Inflammation factors have been extensively studied as relevant prognostic indicators in patients with GC. The neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), the Glasgow prognostic score (GPS), the systemic immune-inflammation index (SII), C-reactive protein (CRP), the serum albumin level, the prognostic nutritional index (PNI), the inflammation-combined prognostic index (ICPI), and the inflammatory burden index (IBI) are associated with survival and can be used as potential prognostic indicators in patients with GC.[10-16]

Biomarkers have gained considerable attention in recent years because of their ability to perform quick, cost-effective, and convenient assessments, which enhances their clinical applicability. The usefulness and efficacy of nutritional and inflammation biomarkers in the treatment of patients with metastatic gastric cancer (mGC) require additional verification.

In this study, we investigated the prognostic significance of inflammatory and nutritional biomarkers measured by conducting blood analysis during the pretreatment period in a cohort of Turkish patients with mGC. The primary aim of conducting this study was to identify the most beneficial biomarker for prognostic evaluation.

MATERIAL AND METHODS

Patients and Data Collection

In this study, we retrospectively included 203 patients diagnosed with mGC from January 2011 to January 2023. We obtained clinicopathological data from patients' databases and medical records. Patients were selected based on the following criteria: 1) histologically confirmed GC; 2) radiologically confirmed metastatic disease; 3) measurement of serum inflammatory and nutritional markers before first-line systemic treatment; and 4) complete medical records. The exclusion criteria were as follows: absence of serum inflammatory and nutritional marker measurements, presence of other malignancies, inadequate clinical outcomes, and signs of active infection or chronic liver disease.

The patient data collected from clinical records included demographic features, Eastern Cooperative Oncology Group performance status (ECOG PS), anatomic location and histopathologic features of the primary tumor, laboratory data before first-line systemic treatment, the number and location of metastases, and the chemotherapy regimens administered. The treatment regimens and dosages used were consistent with those used in the main clinical trials.

Ethical Approval

This study was conducted according to the principles of the Declaration of Helsinki and was approved by İstanbul University-Cerrahpaşa the Local Ethics Committee for clinical trials (date: August 14, 2024; no: 1064826). Owing to the retrospective nature of this study, the requirement for informed consent was waived. As this was a retrospective study, the need for informed permission was waived.

Definitions of Inflammatory and Nutritional Biomarkers

Data on neutrophil, lymphocyte, platelet, albumin, CRP, alkaline phosphatase, and lactate dehydrogenase levels were obtained from peripheral blood tests in the database. Additionally, the PLR, NLR, SII, PNI, CRP-to-albumin ratio (CAR), IBI, body mass index (BMI), and modified GPS (mGPS) were calculated.

The values of the subsequent variables were calculated based on these results. We measured the NLR by dividing the neutrophil count by the lymphocyte count, the PLR by dividing the platelet count by the lymphocyte count, and the CAR by dividing the CRP level by the albumin level. The SII was computed as the neutrophil count×platelet count/total lymphocyte count; the IBI score was computed as the absolute value of CRP×NLR; the PNI was determined as 10×serum albumin level+0.005×total lymphocyte count; the mGPS was assessed with the serum CRP and albumin levels: CRP >10 mg/L and albumin <3.5 g/dL received a score of 2; CRP >10 mg/L or albumin ≥3.5 g/dL received a score of 1; CRP ≤10 mg/L or albumin <3.5 g/dL received a score of 1; and finally, CRP ≤10 mg/L and albumin ≥3.5 g/dL received a score of 0.

Statistical Analysis

The patients were categorized into distinct groups according to systemic inflammatory and nutritional biomarkers, including the NLR, PLR, CAR, SII, IBI, PNI, and BMI. Finally, a survival analysis was conducted on the aforementioned groups. SPSS version 26 was used to conduct the statistical assessment. We analyzed the data using conventional descriptive statistics, which included the mean, standard deviation, median, and range for continuous variables, as well as the frequency and proportion for categorical variables. To analyze categorical data, the Fisher or chi-squared test was conducted, and to analyze continuous data, a t-test was conducted to compare patient features. OS was described as the duration from the start of palliative therapy until death due to any reason or the final visit. The Kaplan-Meier method was used to estimate survival curves, and the log-rank test was conducted for comparisons. Univariate and multivariate logistic regression models were used to evaluate the factors

that contribute to OS. The Cox proportional hazards model was used to conduct a multivariate analysis to evaluate the effect of prognostic factors on OS. All results were considered to be statistically significant at $p<0.05$.

RESULTS

Characteristics of Patients

The median age of patients was 59 years (range: 21-82). There were 144 (71%) male patients and 59 (29%) female patients. The ECOG PS was 0 in 24% (n=49) of the patients, 1 in 70% (n=141), and ≥2 in 6% (n=13) of the patients. The initial demographic and clinicopathologic findings of the patients are summarized in Table 1. Among all patients, 143 (60%) had tumors in the stomach, whereas 60 (30%) had tumors in the gastroesophageal junction. According to the Lauren classification, most patients presented with diffuse-type tumors. The signet ring cell component was present in 41% of patients, and the mucinous component was present in 29% of patients. Most patients (75.4%) were human epidermal growth factor receptor type 2 (HER2)-negative, and 24.6% of patients (n=50) were HER2-positive. Synchronous metastases were present in 158 (78%) patients. The most prevalent metastatic sites were distant lymph nodes, the liver, and the peritoneum (62.1%, 43.3%, and 34.5%, respectively). According to the mGPS assessment, 33% (n=66) of patients scored 0, 49% (n=98) of patients scored 1, and 18% (n=34) of patients scored 2. The calculated nutritional and inflammation markers and scores are summarized in Table 2.

Treatment Interventions

The initial chemotherapy regimens for the patients included 5-fluorouracil plus oxaliplatin (n=99, 49.1%), 5-Fluorouracil plus cisplatin (n=85, 41.6%), Capecitabine plus oxaliplatin (n=14, 6.9%), weekly Paclitaxel (n=3, 1.4%), and 5-Fluorouracil plus Irinotecan (n=2, 1%). In the HER2-positive cohort, 94% of patients (47 of 50) received anti-HER2 treatment (Trastuzumab), whereas three patients were treated with chemotherapy combined with trastuzumab as second-line treatment. In total, 12 patients (5.8%) were administered immune checkpoint inhibitors in combination with chemotherapy as first-line therapy. Only 6 patients, four from the HER-positive group, continued first-line treatment by the evaluation cutoff date.

Second-line chemotherapy was administered to 110 patients, representing 54.4% of the cohort. The most common second-line treatment regimens included 5-Fluorouracil combined with Irinotecan (n=64, 58.1%) and weekly Paclitaxel (n=23, 20.9%). Eight patients were administered Paclitaxel in combination with Ramucirumab, while 2 patients were administered Pembrolizumab.

Survival Analyses

We found that 18 of 202 patients (8.9%) were alive at the last follow-up date. The median follow-up duration was 13.9 (range: 2.7-114.9) months. The last follow-up date was May 1, 2024. According to receiver operating characteristic analysis, no statistically significant cut-off level was found to predict survival for inflammation and nutritional markers (Figure 1). Therefore, patients were categorized into subgroups based on the median levels of the markers (NLR, PLR, PNI, SII, CAR, and IBI), and the variables affecting survival were assessed. Among the inflammatory and nutritional biomarkers, only the mGPS was significantly associated with OS. Patients with mGPS of 0-1 had better OS than those with mGPS of 2 (18.2 vs. 13.4 months, $p<0.001$). In the univariate analysis, ECOG PS (≥1 vs. 0), BMI (<23.20 kg/m^2 vs. ≥23.20 kg/m^2), serum albumin level (<3.5 g/dL vs. ≥3.5 g/dL), and mGPS (2 vs. 0-1) were associated with worse OS. The Kaplan-Meier curves of OS are shown in Figure 2. The multivariate analysis indicated that ECOG PS ≥1 vs. 0 [hazard ratio (HR: 1.5, 95% confidence interval (CI): 1.07-2.48; p=0.018], BMI <23.20 kg/m^2 vs. ≥23.20 kg/m^2 (HR: 0.70, 95% CI: 0.53-0.98; p=0.037), and mGPS 2 vs. 0-1 (HR: 1.3, 95% CI: 1.1-1.7; p=0.001) were independently associated with worse OS. The univariate and multivariate analyses are summarized in Table 3.

DISCUSSION

In this study, we assessed the effect of systemic inflammatory and nutritional factors, including the NLR, PLR, SII, CAR, IBI, mGPS, BMI, and PNI, on survival outcomes in patients

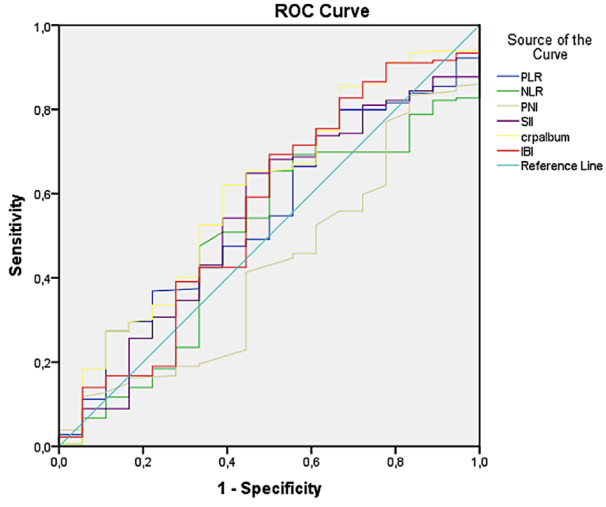

FIGURE 1: Receiver operating characteristic analysis for the inflammation and nutrition-based markers.

ROC: Receiver operating characteristic; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index; CAR: C-reactive protein-to-albumin ratio; IBI: Inflammatory burden index.

diagnosed with mGC. Our findings indicated that the ECOG PS, serum albumin level, BMI, CAR, and mGPS were significantly associated with OS in patients with mGC. Moreover, the results of our analysis revealed that the ECOG PS, BMI, and mGPS were significantly correlated with OS, independent of other predictive factors.

The systemic inflammatory response affects oncological outcomes in cancer patients. Additionally, the nutritional status of patients also plays a significant role in influencing tumor progression.[17] The relationship among systemic inflammation, nutritional status, and cancer patient prognosis involves complex mechanisms and is not fully understood. Several studies have investigated the effect of inflammation and nutritional markers on survival and prognosis in patients diagnosed with GC.[18-21] A meta-analysis involving 18,348 patients demonstrated that an increase in CRP levels, NLR, and GPS/mGPS is correlated with worse survival outcomes in GC patients.[18] Another meta-analysis involving 1,336 patients with advanced GC undergoing immunotherapy revealed that elevated NLR and PLR were correlated with shorter OS.[19] A comprehensive analysis of 14,403 patients across 25 studies indicated that a low preoperative PNI might be associated with a significant occurrence of postoperative complications and an unfavorable prognosis in patients with GC.[20] A retrospective study conducted by Sugiyama et al.[21] showed that active nutritional support can improve the prognosis of patients with mGC undergoing chemotherapy.

Several studies have shown that low albumin levels are significantly correlated with reduced survival rates in GC patients.[22,23] GC patients frequently exhibit poor nutritional status due to tumor infiltration of the stomach or pyloric stenosis, resulting in low serum albumin levels. Additionally,

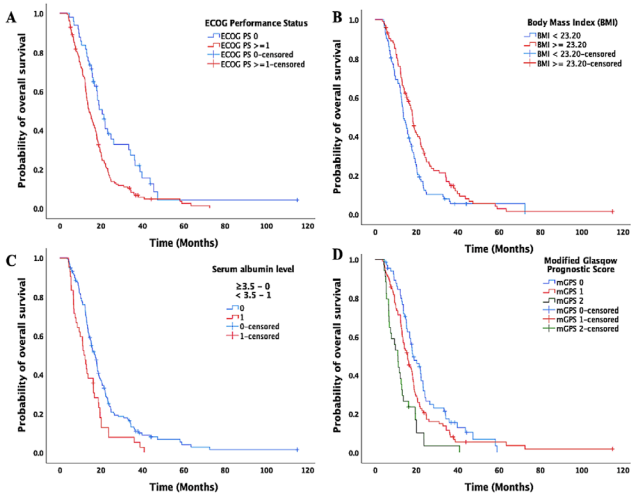

FIGURE 2: Kaplan-Meier: *Eastern Cooperative Oncology Group performance status*.

A; Body mass index B; Serum albumin levels C; and modified Glasgow Prognostic Score (mGPS) D; ECOG: Eastern Cooperative Oncology Group; PS: Performance status; OS: Overall survival; BMI: Body mass index; mGPS: Modified Glasgow prognostic score.

TABLE 1: Baseline demographic and clinicopathologic findings.

Variables (n=203)		n (%)
Age (years)	Median	59 (range 21-82)
	<65	135 (67)
	≥65	68 (33)
Gender	Female	59 (29)
	Male	144 (71)
ECOG PS	PS 0	49 (24)
	PS 1	141(70)
	PS≥2	13(6)
BMI (kg/m^2) (median)		23.20 (range: 14.4-37.6)
Location	Gastroesophageal junction	60 (30)
	Stomach	143 (70)
Lauren classification	Diffuse	112 (55)
	Intestinal	56 (28)
	Unknown	35 (17)
Signet ring cell component		84 (41)
Mucinous component		58 (29)
Microsatellite instabilty-high		2 (1)
HER-2 status	Negative	142 (70)
	Positive	50 (25)
	Unknown	11 (5)
CEA	>ULN	103 (56)
	≤ULN	80 (44)
CA 19-9	>ULN	102 (56)
	≤ULN	81 (44)
De novo metastastasis		158 (78)
Metastatic site, n (%)	Liver	88 (43)
	Peritoneum	70 (35)
	Lung	29 (14)
	Distant lymp nodes	126 (62)
	Bone	23 (11)
	Others	14 (7)
Status	Alive	18 (9)
	Exitus	185 (91)
OS (months)	Median	15.9 (95% CI: 13.7-18.1)

ECOG PS: Eastern Cooperative Oncology Group performance status; BMI: Body mass index; HER2: Human epidermal growth factor receptor type 2; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; ULN: Upper limit of normal; OS: Overall survival.

hypoalbuminemia can appear because of an ongoing systemic inflammatory response, which can negatively affect cancer-specific survival in patients with GC. Elevated CRP levels indicate increased systemic inflammation; consequently, the CAR can be used as a marker for systemic inflammation and nutritional status. A meta-analysis including 3,102 patients from 8 observational studies showed that a high pretreatment CAR was significantly correlated with reduced survival rates ($p<0.001$) for patients with GC.[24] Similar to the findings in other studies, our findings indicated that low albumin levels and high CAR significantly correlate with poorer survival outcomes.

The ECOG PS is a basic tool for determining the physical condition of patients and provides a generally accepted prognostic factor for predicting survival outcomes in cancer patients.[25] A study by Fanotto et al.[26] included 704 mGC patients and reported that patients with an ECOG PS of 2 had significantly shorter progression-free survival and OS than those with PS of 1 and 0. Another study investigating patients with mGC reported that an ECOG PS ≥2 was an independent poor prognostic factor for predicting OS.[27] The results of our study also indicated that patients with an ECOG PS of 0 had significantly better OS than those with an ECOG PS of ≥1.

Patients with mGC often exhibit a generalized loss of skeletal muscle mass and strength, which is frequently attributed to nutritional deficiencies caused by tumor localization and tumor-related inflammation. A meta-analysis conducted by Borggreve et al.[28] that included 4,887 patients with GC showed that patients with low muscle mass had significantly higher rates of postoperative complications, severe postoperative complications, and overall mortality. BMI can serve as a reliable indicator for assessing the nutritional status of cancer patients. The relationship between BMI and survival outcomes in patients with GC is under investigation. Feng et al.[29] examined the relationship between BMI and outcomes in 1,210 patients treated with D2 gastrectomy and revealed that a lower BMI was associated with a reduced incidence of postoperative fever and poorer survival outcomes. Another study evaluated 7,765 patients with GC who underwent surgery at a single institution. Patients with a BMI of 23-30 kg/m^2 before gastrectomy showed better OS and disease-specific survival rates than those with a BMI of <23 kg/m^2.[30] This study also revealed a significant relationship between low BMI (<23.20 kg/m^2) and poor OS in patients with mGC.

TABLE 2: Results of systemic inflammatory and nutritional marker analysis in the cohort.

Variables		Median (range)
LDH		195 (13-2318)
ALP		94 (26-2271)
CRP		11 (0.1-227)
Albumin		4.0 (2.3-5.1)
NLR		2.98 (0.21-65)
PLR		207.2 (45-3710)
PNI		47.5 (13-63)
SII		105.01 (2.66-2411.5)
CAR		2.75 (0.02-81.07)
IBI		34.45 (0.13-2814)
mGPS, n (%) (n=198)	0	66 (33)
	1	98 (49)
	2	34 (18)

LDH: Lactate dehydrogenase; ALP: Alkaline phosphatase; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio (PLR); PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index; CAR: C-reactive protein-to-albumin ratio; IBI: Inflammatory burden index; mGPS: Modified Glasgow prognostic score.

The mGPS is a well-documented inflammation-based prognostic assessment of survival for different types of cancer, including GC.[27,31-34] In previous studies, the predictive value of the mGPS in GC has been investigated mostly in patients with early-stage and locally advanced-stage disease. Zhang et al.[35] investigated 488 GC patients who underwent curative surgery and had normal preoperative serum levels of Carcinoembryonic antigen and Carbohydrate antigen 19-9 to assess the prognostic value of the mGPS for OS. They found significant differences among patients with mGPS of 0, 1, and 2 ($p<0.001$), indicating that a higher mortality rate was associated with a higher mGPS. The results of a meta-analysis including 3,206 GC patients across seven studies showed that OS was significantly lower in patients with mGPS of 1 and 2 than in patients with a score of 0 ($p<0.01$).[36] Demirelli et al.[27] evaluated the relationship between nutritional/inflammatory markers and survival in patients with mGC and revealed that mGPS, PNI, and ECOG scores were independent indicators of shorter survival. Similarly, the results of this study indicated that the mGPS is an independent negative predictive biomarker affecting OS in mGC patients.

Study Limitations

The results obtained in this single-center, real-world study should be interpreted with caution as this study had several limitations. The retrospective collection of data from clinical databases can reveal potential selection biases and influencing factors that may affect the interpretation of the results. Second, we could not control for certain potential cofactors influencing inflammation-related and/or nutritional markers. The incorporation of these parameters in future prospective studies may facilitate a more comprehensive evaluation of the prognostic and predictive importance of inflammatory and nutritional biomarkers in mGC patients.

TABLE 3: Univariate and multivariate analyses of overall survival in advanced gastric cancer patients.

		Median OS (95% CI)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	p value	HR (95% CI)	p value
Gender	Female	17.1 (13.8-20.5)	1.2 (0.9-1.7)	0.15		
	Male	15.6 (13.1-18.0)				
Age	<65	15.5 (13.4-17.6)	0.8 (0.6-1.2)	0.44		
	≥65	16.6 (12.1-21.2)				
ECOG PS	PS 0	20.4 (16.0-24.8)	1.7 (1.2-2.5)	**0.001**	1.5 (1.07-2.48)	**0.018**
	PS ≥1	14.0 (12.1-15.9)				
BMI, kg/m^2	≥23.20	18.1 (16.1-20.0)	0.66 (0.4-0.89)	**0.006**	0.70 (0.53-0.98)	**0.037**
	<23.20	13.7 (11.9-15.4)				
Serum albumin	≥3.5 g/dL	17.1 (15.01-19.1)	1.7 (1.2-2.4)	**0.002**	0.89 (0.3-1.8)	0.76
	<3.5 g/dL	11.6 (9.6-13.6)				
NLR	<2.98	16.2 (13.8-18.6)	1.1 (0.8-1.5)	0.42		
	≥2.98	14.3 (11.4-17.1)				
PLR	<207.2	17.5 (15.0-19.5)	1.2 (0.9-1.6)	0.17		
	≥207.2	13.9 (11.5-16.3)				
PNI	≥47.5	17.7 (15.7-19.8)	0.7 (0.5-1.05)	0.16		
	<47.5	13.9 (11.5-16.3)				
SII	<105.01	16.1 (14.2-18.8)	1.1 (0.8-1.5)	0.39		
	≥105.01	14.0 (11.5-16.5)				
CAR	<2.75	17.8 (16.2-19.5)	1.4 (1.08-1.9)	**0.013**	1.2 (0.8-1.6)	0.26
	≥2.75	13.0 (11.6-14.3)				
IBI	<34.45	17.1 (15.4-18.8)	1.2 (0.9-1.6)	0.13		
	≥34.45	13.4 (10.8-16.1)				
mGPS	0-1	18.2 (13.8-22.5)	1.4 (1.2-1.7)	**<0.001**	1.3 (1.1-1.7)	**0.001**
	2	13.4 (11.2-15.6)				

ECOG: Eastern Cooperative Oncology Group; PS: performance status; OS: Overall survival; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index; CAR: C-reactive protein-to-albumin ratio; IBI: Inflammatory burden index; mGPS: Modified Glasgow prognostic score.

CONCLUSION

The optimal inflammatory and nutritional scoring system for assessing the prognosis of patients with mGC is under investigation. The primary objective of this study was to identify the best biomarker for predicting the prognosis of patients with mGC, and our findings suggested that BMI and mGPS may be the most effective biomarkers for predicting survival outcomes.

Ethics

Ethics Committee Approval: This study was conducted according to the principles of the Declaration of Helsinki and was approved by İstanbul University-Cerrahpaşa the Local Ethics Committee for clinical trials (date: August 14, 2024; no: 1064826).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Idea/Concept: M.G., Ö.A.; Design: M.G., M.Gü., Control/Supervision: Ö.A., N.S.D., Data Collection and/or Processing: M.C.F., S.S., Analysis and/or Interpretation: M.G., Ö.A., Literature Review: G.A.Ş., M.Gü., Writing the Article: M.G., Critical Review: Ö.A., References and Fundings: M.G., N.S.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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