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Research Article

Prognostic Value of Nutritional Status and Early Tumor Marker Dynamics in Metastatic Gastric Cancer

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Abstract

Objectives: Prognostic assessment in metastatic gastric cancer remains challenging because survival is influenced by both tumor biology and host-related clinical condition. This study evaluated the prognostic value of baseline prognostic nutritional index (PNI), early CA19-9 dynamics, and a simple composite score for overall survival stratification.

Methods: This retrospective cohort study included patients with histologically confirmed metastatic gastric adenocarcinoma treated at a single tertiary oncology center. Baseline clinicopathological, laboratory, treatment, and survival data were collected from institutional records. PNI was calculated from serum albumin and peripheral lymphocyte count. Early CA19-9 change was defined as the percentage change between baseline and early follow-up values. Landmark-restricted analyses were used for tumor marker kinetics. A composite score was constructed using two adverse factors: low baseline PNI and insufficient CA19-9 decline. Overall survival was analyzed using Kaplan–Meier and Cox regression models.

Results: Among 126 patients, 95 had available data for both baseline PNI and early CA19-9 kinetics. High-risk patients had shorter median overall survival than low/intermediate-risk patients: 8 versus 14 months, respectively (log-rank p=0.028). In multivariable analysis, a high composite score remained independently associated with inferior overall survival (adjusted HR: 3.05, 95% CI: 1.66–5.62; p<0.001).

Conclusion: A composite score integrating baseline PNI and early CA19-9 dynamics may provide clinically useful survival stratification in metastatic gastric cancer.

Keywords: CA19-9, composite prognostic score, metastatic gastric cancer; overall survival, prognostic nutritional index, tumor marker kinetics

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Gastric cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide, with a substantial proportion of patients diagnosed at an advanced or metastatic stage.[1] Despite improvements in systemic treatment, the prognosis of metastatic gastric cancer remains heterogeneous. Current therapeutic decision-making increasingly incorporates clinicopathological and molecular factors, including HER2 status, PD-L1 expression, microsatellite instability, and patients' performance status.[2] The introduction of HER2-targeted therapy and immune checkpoint inhibitor-based combinations has improved outcomes in selected subgroups; however, many patients still experience early disease progression or limited survival despite standard first-line systemic treatment.[3,4] Therefore, simple and clinically applicable prognostic tools are still needed to better stratify patients at treatment initiation and during early treatment follow-up.

Prognosis in metastatic gastric cancer is determined not only by tumor biology and treatment sensitivity, but also by host-related factors such as nutritional reserve, systemic inflammation, and immune competence. Malnutrition is common in gastric cancer because of tumor-related anorexia, impaired oral intake, gastric outlet symptoms, systemic inflammation, and cancer cachexia. These factors may reduce tolerance to systemic therapy and contribute to inferior survival. Among routinely available laboratory-based indices, the prognostic nutritional index (PNI), calculated from serum albumin and peripheral lymphocyte count, has attracted attention as an integrated marker of nutritional and immune status. Previous studies have shown that a low PNI is associated with poorer outcomes in gastric cancer and other gastrointestinal malignancies.[5–8] Although PNI is not a tumor-specific biomarker, its clinical value lies in its ability to reflect the patient's baseline biological reserve using inexpensive and reproducible laboratory parameters.

In addition to baseline performance status, early treatment response is another key determinant of outcome in metastatic gastric cancer. Radiological response assessment remains the standard method for evaluating treatment efficacy, but imaging is usually performed after several cycles of systemic therapy. In routine clinical practice, serum tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are frequently measured during treatment follow-up. Although baseline tumor marker levels may be influenced by tumor burden, secretion status, and biological heterogeneity, dynamic changes during therapy may provide useful information regarding early treatment sensitivity. Several studies have suggested that declines in CA19-9 and/or CEA during systemic chemotherapy are associated with better treatment response and survival outcomes in advanced gastric cancer.[9,10] Nevertheless, tumor marker kinetics alone may not fully capture patient prognosis, particularly when baseline tumor marker levels are low or noninformative.

Because metastatic gastric cancer is biologically and clinically heterogeneous, single prognostic variables may be insufficient to reflect the complexity of the disease course. Composite approaches that integrate different prognostic domains may provide more clinically meaningful risk stratification than isolated markers. Inflammation- and nutrition-based models have demonstrated prognostic relevance in several cancer populations, supporting the concept that a patient's systemic condition adds important information beyond tumor-related characteristics.[11–13] However, few simple models combine baseline host reserve with early biochemical treatment response in patients with metastatic gastric cancer.

Therefore, this study aimed to evaluate the prognostic value of baseline PNI and early CA19-9 dynamics in patients with metastatic gastric cancer receiving systemic therapy. We further sought to construct a simple composite prognostic score integrating these two routinely available parameters and to assess whether this score could stratify overall survival beyond established clinicopathological factors.

Methods

Study Design and Patient Population

This retrospective cohort study was conducted at the Department of Medical Oncology, İstanbul Medeniyet University Göztepe Training and Research Hospital, Istanbul, Türkiye. Patients diagnosed with gastric cancer between January 2018 and December 2025 were screened through the institutional oncology archive.

During the study period, 630 patients with gastric cancer were identified. Among these, 224 patients had metastatic disease either at initial diagnosis or during follow-up. Patients were eligible for inclusion if they had histologically confirmed gastric adenocarcinoma, documented metastatic disease, available clinical and laboratory records at the time of metastatic diagnosis, and survival follow-up data. After exclusion of patients with incomplete essential data, 126 patients were included in the final full-cohort analysis.

For analyses involving early tumor marker kinetics, a landmark-restricted approach was used to reduce guarantee-time bias. Patients who died within the first 3 months after metastatic diagnosis were excluded from tumor marker kinetic analyses. Among the remaining patients, those with available baseline and early follow-up carbohydrate

antigen 19-9 (CA19-9) measurements were included in the CA19-9 kinetic analysis. Patients with available data for both baseline prognostic nutritional index (PNI) and CA19-9 kinetics were included in the composite score analysis.

Overall survival (OS) was defined as the time from the date of metastatic diagnosis to death from any cause or last follow-up. Patients who were alive at the last follow-up were censored.

Data Collection and Clinical Variables

Clinical, pathological, treatment-related, and laboratory data were retrospectively extracted from electronic medical records. Demographic and clinical variables included age at diagnosis, sex, Eastern Cooperative Oncology Group (ECOG) performance status, smoking history, alcohol use, body mass index (BMI), comorbidities, prior gastrectomy, date of initial diagnosis, date of metastatic diagnosis, and timing of metastatic presentation.

Metastatic presentation was categorized as *de novo* metastatic disease or metachronous metastatic disease. Primary tumor localization was categorized as proximal, middle, or distal gastric cancer according to the anatomical site documented in pathology, endoscopy, radiology, or clinical records. Tumor grade was recorded where available.

HER2 status was determined according to standard pathological criteria. HER2 positivity was defined as immunohistochemistry (IHC) 3+ staining or IHC 2+ staining with confirmatory *in situ* hybridization (ISH) positivity. Programmed death-ligand 1 (PD-L1) expression was recorded using the combined positive score (CPS) when available. Microsatellite instability (MSI) status was also recorded when available.

The presence of metastatic involvement was documented for liver, peritoneum, lung, bone, and distant lymph nodes. Treatment-related variables included first-line systemic treatment regimen, number of treatment cycles, treatment response, second-line treatment when available, and treatment discontinuation status.

Laboratory Parameters and Derived Indices

Baseline laboratory parameters obtained at or near the time of metastatic diagnosis were recorded. These included hemoglobin, red blood cell count, hematocrit, red cell distribution width, white blood cell count, neutrophil count, lymphocyte count, platelet count, monocyte count, serum albumin, lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), and CA19-9.

The prognostic nutritional index was calculated using the following formula:

PNI=10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (/mm^3)

The neutrophil-to-lymphocyte ratio was calculated as:

NLR=absolute neutrophil count / absolute lymphocyte count

The systemic immune-inflammation index was calculated as:

SII= (platelet count × neutrophil count) / lymphocyte count

Early tumor marker kinetics were evaluated using CEA and CA19-9 values obtained at baseline and at the first early reassessment during systemic treatment. Percentage change was calculated as:

Tumor marker change (%) =[(baseline value – follow-up value) / baseline value] ×100

Accordingly, positive values indicated a decrease in tumor marker level, whereas negative values indicated an increase during treatment.

Definition of the Composite Prognostic Score

A composite prognostic score was constructed using two routinely available parameters: baseline PNI and early CA19-9 change. These variables were selected because they represent complementary prognostic domains: baseline nutritional and immune reserve, and early biochemical tumor response to systemic therapy.

Cut-off values were determined using median values in the evaluable study cohort, as no universally accepted cut-off values for PNI or early CA19-9 percentage change have been established in this specific clinical context. This approach was selected to provide a simple, reproducible, and exploratory risk stratification method suitable for retrospective analysis. Low PNI was defined as a PNI below the cohort median. Insufficient CA19-9 response was defined as a CA19-9 change below the cohort median, indicating an inadequate decline or an increase in CA19-9 during early treatment.

One point was assigned for each adverse factor:

- Low baseline PNI
- Insufficient CA19-9 decline

The composite score therefore ranged from 0 to 2. For survival analysis, patients were grouped as follows:

- Low/intermediate risk: score 0–1
- High risk: score 2

This grouping was selected because preliminary Kaplan–Meier analysis showed overlapping survival curves for scores 0 and 1, whereas patients with a score of 2 demonstrated distinctly inferior survival.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY,

USA). Continuous variables were assessed for normality using visual methods, including histograms and Q–Q plots, as well as analytical methods where appropriate. Because most continuous variables were not normally distributed, they were summarized as median and interquartile range (IQR). Categorical variables were summarized as frequencies and percentages.

Comparisons between groups were performed using the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Overall survival was estimated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. Univariable Cox proportional hazards regression analyses were performed to evaluate the association between clinicopathological variables, laboratory parameters, tumor marker kinetics, and overall survival. Variables with clinical relevance and/or a p-value below 0.10 in univariable analysis were considered for multivariable Cox regression models.

Two multivariable Cox regression models were planned. The first model evaluated the independent prognostic value of baseline PNI and early CA19-9 change as continuous variables after adjustment for relevant clinicopathological factors. The second model evaluated the prognostic impact of the composite score after adjustment for established prognostic variables, including HER2 status, primary tumor localization, and ECOG performance status. Hazard ratios (HRs) were reported with 95% confidence intervals (CIs). All statistical tests were two-sided, and a p-value below 0.05 was considered statistically significant.

Ethics Statement

The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Göztepe Prof. Dr. Süleyman Yalçın City Hospital (Approval date: April 22, 2026; Approval number: 2026/0172). The study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki. Because of the retrospective design of the study and the use of anonymized patient data, the requirement for written informed consent was waived by the ethics committee.

Results

Patient Flow and Analysis Populations

A total of 630 patients with gastric cancer were screened from the institutional oncology archive. Among these, 224 patients had metastatic disease either at initial diagnosis or during follow-up. After exclusion of patients with incomplete essential clinical, laboratory, or survival data, 126 patients with metastatic gastric adenocarcinoma were included in the full study cohort.

For analyses involving early tumor marker kinetics, a landmark-restricted approach was applied to reduce guarantee-time bias. Four patients who died within the first 3 months after metastatic diagnosis were excluded from these analyses, leaving 122 patients eligible for landmark-restricted assessment. Among these, 96 patients had available baseline and early follow-up carbohydrate antigen 19-9 (CA19-9) measurements. One patient was excluded because of missing prognostic nutritional index (PNI) data; therefore, 95 patients were included in the composite prognostic score analysis. Complete-case multivariable Cox regression analysis was performed in 91 patients for the model including continuous PNI and CA19-9 change, and in 84 patients for the model including the composite score, HER2 status, primary tumor localization, and Eastern Cooperative Oncology Group (ECOG) performance status (Fig. 1).

Baseline Characteristics of the Full Cohort

The baseline characteristics of the full cohort are summarized in Table 1. The median age was 66 years (interquar-

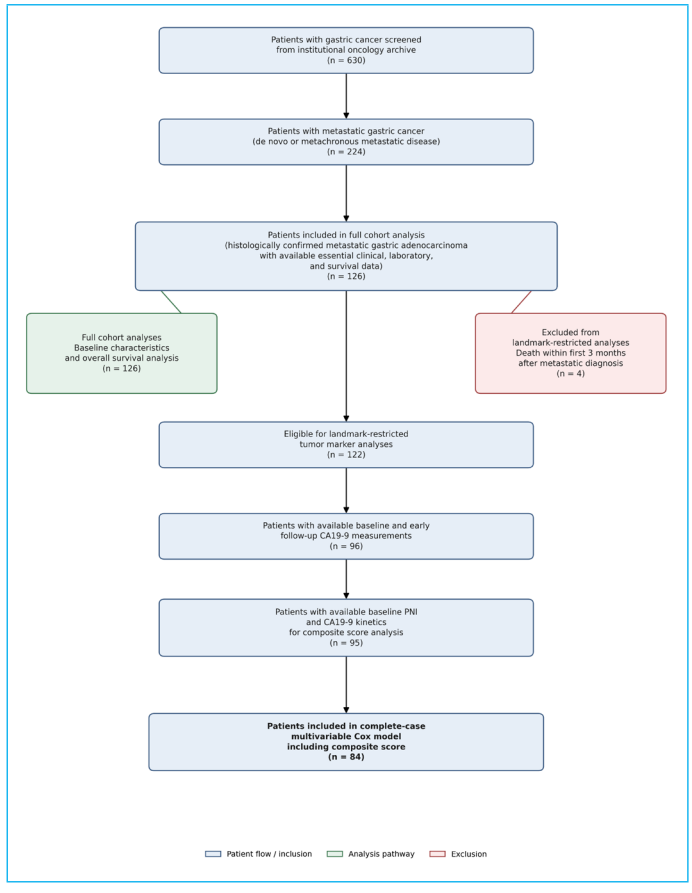

Figure 1. Patient flow diagram and analysis populations.

Table 1. Baseline characteristics of the full cohort

Characteristic	Overall cohort, n=126
Demographics and clinical characteristics	
Age, years	66 (56–73)
Male sex	86 (68.3%)
Female sex	40 (31.7%)
ECOG PS 0	74 (58.7%)
ECOG PS ≥1	52 (41.3%)
BMI, kg/m^2	24.2 (21.3–26.8)
De novo metastatic disease	90 (71.4%)
Metachronous metastatic disease	36 (28.6%)
Prior gastrectomy	48 (38.1%)
Tumor characteristics	
Proximal tumor location	37/118 (31.4%)
Middle gastric location	46/118 (39.0%)
Distal tumor location	35/118 (29.7%)
Tumor location unavailable	8 (6.3%)
Grade 1	4/121 (3.3%)
Grade 2	56/121 (46.3%)
Grade 3	61/121 (50.4%)
HER2-positive disease	17/119 (14.3%)
HER2-negative disease	102/119 (85.7%)
PD-L1 CPS available	47 (37.3%)
PD-L1 CPS, median among available patients	1.0 (0.0–3.4)
MSI status available	80 (63.5%)
Microsatellite stable / MSS	76/80 (95.0%)
MSI-high	4/80 (5.0%)
Metastatic sites	
Liver metastasis	47 (37.3%)
Peritoneal metastasis	62 (49.2%)
Lung metastasis	10 (7.9%)
Bone metastasis	17 (13.5%)
Distant lymph node metastasis	82 (65.1%)
First-line systemic treatment	
Platinum–fluoropyrimidine chemotherapy	74 (58.7%)
HER2-targeted chemotherapy	15 (11.9%)
FOLFIRI	10 (7.9%)
Taxane-based chemotherapy	10 (7.9%)
Fluoropyrimidine monotherapy	8 (6.3%)
Immunotherapy-based regimen	5 (4.0%)
FLOT	4 (3.2%)
Baseline laboratory parameters	
Hemoglobin, g/dL	10.6 (9.3–12.6)
Albumin, g/dL	3.7 (3.2–4.1)
PNI	45.5 (39.0–49.9)
NLR	3.75 (2.27–5.71)
SII	1,082,485 (636,227–1,727,455)
CEA, ng/mL	5.1 (1.9–13.7)
CA19-9, U/mL	26.2 (9.1–153.0)
Survival status	
Deaths	104 (82.5%)
Overall survival, months	11 (6–19)

Data are presented as median (interquartile range) for continuous variables and n (%) for categorical variables. Percentages were calculated using the full cohort as the denominator unless otherwise stated. For variables with missing data, the number of evaluable patients is shown. BMI: Body mass index; ECOG PS: Eastern Cooperative Oncology Group performance status; HER2: Human epidermal growth factor receptor 2; PD-L1 CPS: Programmed death-ligand 1 combined positive score; MSI: Microsatellite instability; PNI: Prognostic nutritional index; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9.

tile range [IQR], 56.2–72.8), and most patients were male (n=86, 68.3%). ECOG performance status was 0 in 74 patients (58.7%), whereas 52 patients (41.3%) had an ECOG performance status of 1 or higher. Median body mass index was 24.2 kg/m^2 (IQR, 21.3–26.8).

Most patients had *de novo* metastatic disease (n=90, 71.4%), while 36 patients (28.6%) developed metachronous metastatic disease during follow-up. Primary tumor localization was proximal in 37 patients, middle gastric in 46 patients, and distal in 35 patients; localization data were unavailable in 8 patients. HER2 status was available in 119 patients, of whom 17 patients (14.3%) were HER2-positive. Programmed death-ligand 1 (PD-L1) combined positive score (CPS) was available in 47 patients, with a median CPS of 1.0; among tested patients, 18 had CPS 0, 18 had CPS 1–5, and 11 had CPS ≥ 6. Microsatellite instability (MSI) status was evaluable in 80 patients; 76 patients had microsatellite-stable disease and 4 patients had MSI-high disease.

The most common metastatic sites were distant lymph nodes (n=82, 65.1%), peritoneum (n=62, 49.2%), and liver (n=47, 37.3%). Lung and bone metastases were present in 10 patients (7.9%) and 17 patients (13.5%), respectively.

The most frequently used first-line systemic treatment was platinum–fluoropyrimidine-based chemotherapy (n=74), followed by HER2-targeted chemotherapy combinations (n=15), taxane-based therapy (n=10), FOLFIRI (n=10), flu-

oropyrimidine monotherapy (n=8), immunotherapy-based regimens (n=5), and FLOT (n=4).

At metastatic diagnosis, median hemoglobin was 10.6 g/dL (IQR, 9.3–12.6), median serum albumin was 3.7 g/dL (IQR, 3.2–4.1), median PNI was 45.5 (IQR, 39.0–49.9), median neutrophil-to-lymphocyte ratio (NLR) was 3.7 (IQR, 2.3–5.7), and median systemic immune-inflammation index (SII) was 1,082,485 (IQR, 636,227–1,727,455). Median baseline carcinoembryonic antigen (CEA) and CA19-9 levels were 5.1 ng/mL (IQR, 1.9–13.7) and 26.2 U/mL (IQR, 9.1–153.0), respectively.

At the time of analysis, 104 patients had died and 22 patients were censored. The median overall survival of the full cohort was 11 months.

Composite Prognostic Score Cohort

Among the 95 patients included in the composite score analysis, the median PNI was 45.5 and the median early CA19-9 change was −7.4%. Because tumor marker percentage change was calculated as:

[(baseline value − follow-up value) / baseline value] × 100

positive values indicated a decrease in CA19-9, while negative values indicated an increase.

One point was assigned for each adverse factor:

1. PNI<45.5
2. CA19-9 change<−7.4% (indicating an insufficient CA19-9 decline or an increase during early treatment)

The composite score ranged from 0 to 2. Scores 0 and 1 showed overlapping survival outcomes and were therefore combined into a low/intermediate-risk group. Accordingly, 75 patients were classified as low/intermediate risk (score 0–1) and 20 patients were classified as high risk (score 2).

Compared with the low/intermediate-risk group, the high-risk group had significantly lower PNI values, worse early CA19-9 dynamics, higher NLR, and a trend toward higher SII. Demographic characteristics, ECOG performance status, HER2 status, tumor localization, and metastatic site distribution were generally balanced between the two groups (Table 2).

Univariable and Multivariable Survival Analyses

Univariable Cox proportional hazards analyses for overall survival are shown in Table 3. Among clinical variables, ECOG performance status ≥ 1 was significantly associated with inferior overall survival. HER2-positive disease was associated with a lower risk of death compared with HER2-negative disease. Primary tumor localization was also significantly associated with survival, with both proximal and middle gastric tumors demonstrating worse outcomes compared with distal tumors.

Among laboratory and dynamic biomarker variables, a higher baseline PNI was associated with improved overall survival. Early CA19-9 change was also significantly associated with survival, indicating that a greater CA19-9 decline during early treatment was associated with a lower risk of death. In contrast, age, sex, body mass index, timing of metastatic presentation, metastatic site distribution, NLR, SII, and CEA change were not significantly associated with overall survival in univariable analysis.

Variables with clinical relevance and/or significant associations in univariable analysis were entered into a multivariable Cox proportional hazards regression model. The results are presented in Table 4. In this complete-case model including 91 patients and 71 events, HER2-positive disease was independently associated with improved overall survival. Primary tumor localization also retained independent prognostic significance, with both proximal and middle gastric tumors associated with worse survival compared with distal tumors.

Among laboratory and dynamic biomarker variables, a higher baseline PNI remained independently associated with improved overall survival. Similarly, a greater early CA19-9 decrease was independently associated with a lower risk of death. ECOG performance status did not retain independent prognostic significance after adjustment for HER2 status, tumor localization, PNI, and CA19-9 change.

The prognostic impact of the composite score was further evaluated in a multivariable Cox proportional hazards model, as shown in Table 5. In this complete-case model including 84 patients and 65 events, patients in the high-risk composite score group had significantly worse overall survival compared with those in the low/intermediate-risk group. After adjustment for HER2 status, primary tumor localization, and ECOG performance status, a high composite score remained independently associated with an approximately three-fold increased risk of death (adjusted HR: 3.05, 95% CI: 1.66–5.62; p<0.001).

HER2-positive disease was independently associated with improved overall survival. Primary tumor localization also retained prognostic significance, with both proximal and middle gastric tumors associated with worse survival compared with distal tumors. ECOG performance status did not remain statistically significant in this adjusted model.

Kaplan–Meier survival analysis according to the composite prognostic score is shown in Figure 2. Patients classified as high risk (score 2) had significantly inferior overall survival compared with those in the low/intermediate-risk group (score 0–1). Median overall survival was approximately 8 months in the high-risk group and 14 months in the low/intermediate-risk group. The difference between the sur-

Table 2. Baseline characteristics according to composite prognostic score

Characteristic	Score 0–1, n=75	Score 2, n=20	p
Demographics and clinical characteristics			
Age, years	63 (57–72)	61 (54–73)	0.424
Male sex	52 (69.3%)	15 (75.0%)	0.621
ECOG PS ≥1	28 (37.3%)	7 (35.0%)	0.848
BMI, kg/m^2	24.1 (21.1–27.5)	25.0 (22.8–26.7)	0.817
De novo metastatic disease	59 (78.7%)	13 (65.0%)	0.243
HER2-positive disease	13 (17.3%)	3 (15.0%)	1.000
Primary tumor location			
Proximal	20 (26.7%)	6 (30.0%)	0.525
Middle gastric	29 (38.7%)	9 (45.0%)	
Distal	21 (28.0%)	3 (15.0%)	
Metastatic sites			
Liver metastasis	28 (37.3%)	4 (20.0%)	0.145
Peritoneal metastasis	38 (50.7%)	9 (45.0%)	0.652
Lung metastasis	5 (6.7%)	0 (0.0%)	0.580
Bone metastasis	8 (10.7%)	3 (15.0%)	0.694
Distant lymph node metastasis	49 (65.3%)	14 (70.0%)	0.830
Tumor markers and laboratory parameters			
Baseline CEA, ng/mL	4.5 (1.7–13.3)	4.4 (2.2–49.6)	0.280
Baseline CA19-9, U/mL	26.1 (6.8–98.7)	36.6 (14.7–286.8)	0.121
CEA change, %	−4.5 (−42.9–44.1)	−95.2 (−148.0 to −3.7)	**0.001**
CA19-9 change, %	0.1 (−30.3–53.5)	−66.5 (−187.0 to −23.6)	**<0.001**
NLR	3.45 (2.19–5.05)	4.37 (3.70–7.02)	**0.005**
SII	902,107 (607,723–1,529,684)	1,264,450 (947,659–1,987,222)	0.051
PNI	47.0 (41.5–50.5)	38.8 (34.5–41.9)	**<0.001**

Data are presented as median (interquartile range) or n (%). The composite prognostic score was constructed using baseline PNI and early CA19-9 change. Low/intermediate risk was defined as score 0–1, and high risk as score 2. Tumor marker change was calculated as [(baseline value − follow-up value) / baseline value] × 100; therefore, positive values indicate a decrease and negative values indicate an increase. P values were calculated using the Mann–Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate. P values for PNI and CA19-9 change should be interpreted cautiously because these variables define the composite score.
BMI: Body mass index; ECOG PS: Eastern Cooperative Oncology Group performance status; HER2: Human epidermal growth factor receptor 2; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9.

vival curves was statistically significant on log-rank testing (log-rank p=0.028; Fig. 2).

Discussion

In this retrospective cohort study of patients with metastatic gastric cancer, we evaluated the prognostic relevance of baseline nutritional status and early tumor marker dynamics using routinely available laboratory parameters. The main finding was that a composite prognostic score integrating baseline prognostic nutritional index (PNI) and early carbohydrate antigen 19-9 (CA19-9) change stratified overall survival (OS) in the composite-score evaluable cohort. Patients with both adverse factors—namely low PNI and insufficient CA19-9 decline or increase during early treatment—had significantly shorter OS than patients with zero or one adverse factor. Importantly, the composite score remained independently associated with OS after adjustment for HER2 status, primary tumor localization, and Eastern Cooperative Oncology Group (ECOG) performance status. These findings suggest that integrating baseline host reserve with early biochemical treatment response may provide a clinically practical approach for risk stratification in metastatic gastric cancer.

The prognostic role of PNI observed in our study is consistent with the biological relationship between nutritional

Table 3. Univariable cox proportional hazards analysis for overall survival

Variable	N	Events	HR	95% CI	p
Demographics and clinical characteristics					
Age, per year	126	104	1.005	0.988–1.023	0.552
Male vs female	126	104	0.973	0.645–1.468	0.896
BMI, per kg/m^2	115	93	0.975	0.935–1.017	0.244
ECOG PS ≥1 vs 0	126	104	1.548	1.051–2.280	**0.027**
De novo vs metachronous metastasis	126	104	1.218	0.782–1.896	0.384
Prior gastrectomy yes vs no	126	104	0.701	0.464–1.058	0.091
Tumor characteristics					
Grade 3 vs grade 1–2	121	100	1.207	0.813–1.794	0.351
HER2-positive vs HER2-negative	119	97	0.529	0.282–0.992	**0.047**
Primary tumor localization, overall	118	97	—	—	**0.020**
Proximal vs distal	118	97	1.923	1.123–3.292	**0.017**
Middle vs distal	118	97	1.913	1.169–3.132	**0.010**
Metastatic sites					
Liver metastasis present vs absent	126	104	0.794	0.532–1.185	0.258
Peritoneal metastasis present vs absent	126	104	0.822	0.559–1.209	0.320
Lung metastasis present vs absent	126	104	0.787	0.382–1.621	0.516
Bone metastasis present vs absent	126	104	1.499	0.878–2.561	0.138
Distant lymph node metastasis present vs absent	126	104	0.823	0.549–1.233	0.345
Laboratory and dynamic biomarker variables					
PNI, per unit increase	125	103	0.971	0.946–0.997	**0.026**
NLR, per unit increase	126	104	1.028	0.991–1.066	0.139
SII, per 100,000-unit increase	126	104	1.005	0.996–1.013	0.271
CEA change, per 10% increase	95	75	0.989	0.975–1.003	0.118
CA19-9 change, per 10% increase	96	76	0.988	0.982–0.994	**<0.001**

Hazard ratios were estimated using univariable Cox proportional hazards regression analysis. Overall survival was measured from the date of metastatic diagnosis to death from any cause or last follow-up. For primary tumor localization, distal tumor location was used as the reference category. Tumor marker change was calculated as [(baseline value − follow-up value) / baseline value] × 100; therefore, positive values indicate a tumor marker decrease and negative values indicate a tumor marker increase. Analyses involving CEA and CA19-9 change were performed in the landmark-restricted population with available paired baseline and early follow-up tumor marker values. BMI: Body mass index; ECOG PS: Eastern Cooperative Oncology Group performance status; HER2: Human epidermal growth factor receptor 2; PNI: Prognostic nutritional index; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9; HR: Hazard ratio; CI: Confidence interval.

status, systemic inflammation, immune competence, and cancer outcomes. PNI combines serum albumin and peripheral lymphocyte count, thereby reflecting both nutritional reserve and immune status. In metastatic gastric cancer, malnutrition may result from reduced oral intake, tumor-related symptoms, systemic inflammation, and cancer cachexia. These factors may impair treatment tolerance, reduce chemotherapy delivery, and contribute to poor survival.[11–14] Previous studies and meta-analyses have reported that a low PNI is associated with inferior outcomes in gastric cancer and other malignancies.[5–8] More recently, inflammation- and nutrition-based biomarkers have also been evaluated in metastatic gastric cancer cohorts, supporting the prognostic relevance of host systemic status in this setting.[15] Our findings add to this literature by showing that PNI retains prognostic value when evaluated alongside early tumor marker kinetics.

Early CA19-9 dynamics were also independently associated with OS in our analysis. This finding is clinically meaningful because changes in serum tumor markers during initial systemic therapy may provide early information about treatment sensitivity before formal radiological reassessment. Previous studies in advanced gastric cancer have suggested that decreases in CA19-9 and/or carcinoembryonic antigen

Table 4. Multivariable cox proportional hazards analysis including Continuous PNI and CA19-9 change

Variable	HR	95% CI	p
Tumor characteristics			
HER2-positive vs HER2-negative	0.396	0.190–0.822	**0.013**
Primary tumor localization, overall	—	—	**0.004**
Proximal vs distal	2.619	1.348–5.089	**0.004**
Middle vs distal	2.464	1.363–4.455	**0.003**
Clinical variable			
ECOG PS ≥1 vs 0	1.047	0.625–1.753	0.863
Laboratory and dynamic biomarker variables			
PNI, per unit increase	0.962	0.930–0.995	**0.024**
CA19-9 change, per 10% increase	0.991	0.985–0.997	**0.005**

Multivariable Cox proportional hazards regression analysis was performed using complete-case data from patients with available PNI, CA19-9 change, HER2 status, tumor localization, ECOG performance status, and survival data. The model included 91 patients and 71 events. Overall survival was measured from the date of metastatic diagnosis to death from any cause or last follow-up. Distal tumor localization and HER2-negative disease were used as reference categories. CA19-9 change was calculated as [(baseline value − follow-up value) / baseline value] × 100; therefore, positive values indicate a decrease and negative values indicate an increase. For CA19-9 change, the hazard ratio is presented per 10% increase.
PNI: Prognostic nutritional index; CA19-9: Carbohydrate antigen 19-9; HER2: Human epidermal growth factor receptor 2; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: Hazard ratio; CI: Confidence interval.

Table 5. Multivariable cox proportional hazards analysis including composite prognostic score

Variable	HR	95% CI	p
Composite prognostic score			
High risk, score 2 vs score 0–1	3.051	1.656–5.619	**<0.001**
Tumor characteristics			
HER2-positive vs HER2-negative	0.334	0.156–0.716	**0.005**
Primary tumor localization, overall	—	—	**0.027**
Proximal vs distal	2.457	1.207–5.004	**0.013**
Middle vs distal	2.409	1.246–4.657	**0.009**
Clinical variable			
ECOG PS ≥1 vs 0	1.478	0.864–2.526	0.154

Multivariable Cox proportional hazards regression analysis was performed using complete-case data from patients with available composite prognostic score, HER2 status, primary tumor localization, ECOG performance status, and survival data. The model included 84 patients and 65 events. Overall survival was measured from the date of metastatic diagnosis to death from any cause or last follow-up. The composite prognostic score was constructed using baseline PNI and early CA19-9 change. Low/intermediate risk was defined as score 0–1, and high risk was defined as score 2. Distal tumor localization, HER2-negative disease, ECOG PS 0, and composite score 0–1 were used as reference categories. HER2: Human epidermal growth factor receptor 2; ECOG PS: Eastern Cooperative Oncology Group performance status; PNI: Prognostic nutritional index; CA19-9: Carbohydrate antigen 19-9; HR: Hazard ratio; CI: Confidence interval.

(CEA) during chemotherapy are associated with treatment response and improved survival outcomes.[9,10] In the present study, patients with insufficient CA19-9 decline or increasing CA19-9 during early treatment had worse survival, supporting the concept that CA19-9 kinetics may serve as a practical surrogate of early biochemical response. However, CA19-9 should not be interpreted as a universal marker in all patients. Its clinical utility may be limited in patients with low baseline values, non-secretor biology, Lewis antigen-negative phenotype, or non-malignant causes of elevation.[16,17] Therefore, CA19-9 kinetics should be interpreted in conjunction with clinical findings and imaging rather than as an isolated determinant of treatment decisions.

The key contribution of this study is the construction of a simple composite score that combines two complementary prognostic dimensions. PNI reflects the patient's baseline host reserve, whereas CA19-9 change reflects early tumor response to systemic therapy. Either parameter alone captures only one aspect of prognosis. A patient with preserved nutritional status may still have aggressive, treatment-resistant disease, while a patient with early tumor

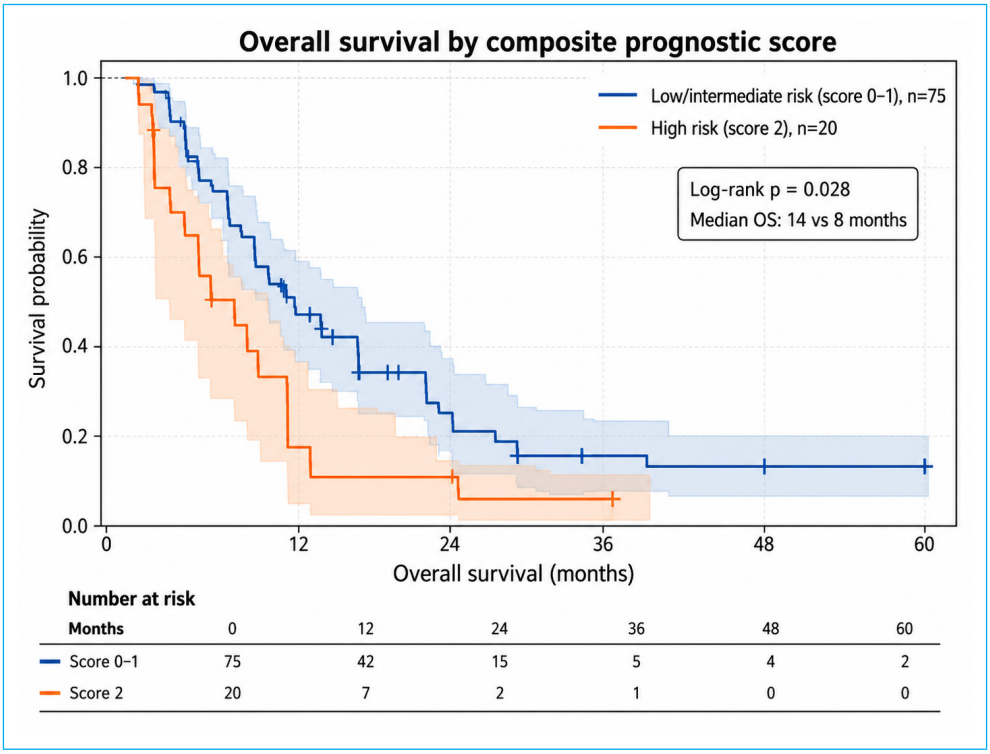

Figure 2. Kaplan–Meier survival curves according to composite prognostic score.

Footnote for Figure 2 Patients were stratified into low/intermediate-risk (score 0–1) and high-risk (score 2) groups based on a composite score integrating baseline prognostic nutritional index and early CA19-9 change. Median overall survival was approximately 14 months in the low/intermediate-risk group and 8 months in the high-risk group. Tick marks indicate censored observations.

marker decline may still have limited survival because of poor baseline reserve or systemic inflammation. By combining these parameters, the composite score may better reflect the interaction between patient condition and tumor behavior. In our cohort, the high-risk group had a median OS of 8 months compared with 14 months in the low/intermediate-risk group, and the difference remained significant in multivariable analysis. Nevertheless, this score should be considered exploratory and hypothesis-generating rather than a validated prognostic model.

HER2 status remained independently associated with OS in our multivariable models. This finding is expected in the modern treatment era, because HER2-positive metastatic gastric cancer represents a biologically distinct subgroup and allows the use of HER2-targeted treatment. The survival benefit of trastuzumab in HER2-positive advanced gastric or gastroesophageal junction cancer was established in the ToGA trial.[3] And subsequent real-world analyses have also suggested better outcomes for HER2-positive patients, particularly when treated with trastuzumab-based therapy.[18] In our study, the persistence of HER2 status as an independent prognostic variable suggests that the composite PNI–CA19-9 score provides information that is not simply a substitute for established tumor biology or treatment-selection factors.

Primary tumor localization also retained prognostic significance in our analysis, with proximal and middle gastric tumors associated with worse survival compared with distal tumors. Gastric cancer is a heterogeneous disease, and anatomical subsite may reflect differences in biology, stage distribution, metastatic pattern, and treatment outcomes. Prior evidence has suggested that proximal gastric cancers may have a less favorable prognosis than distal tumors, although the magnitude of this effect can vary according to stage, cohort composition, and treatment setting.[19] Our findings support the view that primary tumor location should be considered when interpreting survival heterogeneity in metastatic gastric cancer. However, because our cohort was relatively small and retrospective, the localization finding should be interpreted cautiously and should not be overemphasized as a stand-alone conclusion.

From a clinical perspective, the proposed composite score may have practical value because it is based on inexpensive, routinely available parameters. Baseline PNI can be calculated from standard blood tests, and CA19-9 is commonly monitored during treatment in gastrointestinal oncology practice. Patients classified as high risk by this score may benefit from closer clinical monitoring, earlier radiological reassessment, proactive nutritional evaluation, and support-

ive care interventions. Nutritional support may be particularly relevant in advanced gastric cancer, where malnutrition and cachexia are common and may affect treatment continuation.[20] Importantly, the score should not be used to deny systemic treatment; rather, it may help identify patients who require more intensive supportive care and closer follow-up.

Study Limitations

This study has several limitations. First, the retrospective and single-center design introduces potential selection bias and limits generalizability. Second, the composite-score analysis included 95 patients, and the complete-case multivariable model included a smaller subset; therefore, the number of events and covariates should be interpreted with caution. Third, the cut-off values for PNI and CA19-9 change were derived from cohort medians. Although this approach is simple, clinically understandable, and reproducible, median-derived cut-offs are cohort-dependent and may not represent biologically optimal or universally generalizable thresholds. Therefore, these cut-off values should be interpreted as exploratory and require validation in independent external cohorts before clinical application. Fourth, CA19-9 kinetics could only be assessed in patients with available paired baseline and early follow-up values, creating a risk of selection bias. Moreover, CA19-9 kinetics may be less informative in patients with low baseline CA19-9 levels or non-secretor biology, and percentage changes may be unstable when baseline values are very low. Therefore, the composite score may be most applicable to patients with measurable and clinically interpretable baseline CA19-9 values. Fifth, although we used a landmark-restricted approach to reduce guarantee-time bias, residual bias may still exist because tumor marker kinetics inherently require patients to survive long enough to undergo early reassessment.[21] Sixth, treatment heterogeneity across the long study period may have influenced outcomes, as patients received different first-line systemic regimens and therapeutic standards for metastatic gastric cancer evolved over time. Therefore, the prognostic performance of the score should be interpreted within the context of a heterogeneous real-world treatment population. Finally, we did not perform external validation, calibration analysis, or formal model-performance testing such as C-index or time-dependent area under the curve (AUC). Therefore, the score should be presented as an exploratory prognostic tool rather than a validated prediction model.[22]

Future studies should validate this composite score prospectively in larger, independent cohorts. Additional analyses should evaluate whether the score performs better in patients with elevated baseline CA19-9, whether alternative CA19-9 thresholds improve prognostic discrimination, and whether serial changes in PNI during treatment add further information. Integration with molecular biomarkers such as HER2, programmed death-ligand 1 (PD-L1) expression, microsatellite instability (MSI) status, and emerging genomic markers may also help refine prognostic stratification. If externally validated, this simple score may be useful for clinical counseling, supportive care planning, and stratification in real-world studies of metastatic gastric cancer. Before routine clinical implementation, this composite score should be externally validated in larger independent cohorts and, ideally, prospectively evaluated.

Conclusion

In conclusion, this study suggests that a composite prognostic score integrating baseline PNI and early CA19-9 dynamics may stratify overall survival in patients with metastatic gastric cancer. The score combines host-related nutritional and immune reserve with early biochemical tumor response, providing a practical framework based on routinely available laboratory parameters. Although external validation is required, this exploratory model may help identify patients at higher risk for poor outcomes and support more individualized clinical monitoring and supportive care.

Disclosure

Ethics Committee Approval: The study was approved by the Ethics Committee of Göztepe Prof. Dr. Süleyman Yalçın City Hospital Non-Interventional Clinical Research Institution on 22.04.2026 date with approval number 2026/0172.

Informed Consent: Because of the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

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