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Original Article

The ımpact of the novel tumor marker ındex (TMI) on survival and prognosis in metastatic gastric cancer

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Abstract: Metastatic gastric cancer has a poor prognosis, highlighting the need for accessible and cost-effective prognostic biomarkers. This study evaluated the prognostic value of a CEA- and CA 19-9-based tumor marker index (TMI) for clinicopathological characteristics, progression-free survival (PFS), and overall survival (OS). This retrospective multicenter study included 400 patients with metastatic gastric adenocarcinoma treated at six centers between 2013 and 2025. CEA and CA 19-9 levels were normalized to their respective upper limits of normal, and TMI was calculated using their geometric mean. Patients were classified according to a ROC-derived TMI threshold of 0.94. Survival was evaluated using Kaplan-Meier analysis and multivariable Cox regression, with sensitivity analyses using alternative TMI specifications. The median age was 64.0 years, 70.5% of patients were male, and 71.5% had de novo metastatic disease. The most common metastatic sites were the peritoneum (47.3%) and liver (43.5%). TMI≥0.94 was associated with shorter OS (13.06 vs. 16.43 months; P=0.048) and PFS (10.53 vs. 14.06 months; P=0.011), although its discriminatory performance was limited (AUC=0.515). In the final center-stratified, treatment-era-adjusted multivariable models, TMI per 1-SD increase was not independently associated with OS (HR=0.920, 95% CI: 0.828-1.023; P=0.124) or PFS (HR=0.930, 95% CI: 0.838-1.032; P=0.170). TMI showed a threshold-dependent association with survival in metastatic gastric cancer, but this association was not confirmed when TMI was modeled continuously. These findings should be considered exploratory and require external validation before clinical application.

Keywords: Metastatic gastric cancer, tumor marker index, carcinoembryonic antigen, carbohydrate antigen 19-9, overall survival, progression-free survival, prognostic biomarker

Introduction

Gastric cancer remains a major global health problem and is currently the fifth most commonly diagnosed malignancy worldwide. It also continues to be a leading cause of cancer-related death [1]. Many patients are diagnosed after the disease has extended beyond the primary site, with regional lymph node involvement or distant organ spread. Across epidemiological series, the proportion of patients presenting with metastatic disease has varied between 35% and 65% [2].

Serum tumor markers may reflect biological processes associated with tumor growth, invasion, and metastatic dissemination [3]. Among the markers used in gastric cancer, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are inexpensive and routinely available in clinical practice, and their concentrations have been associated with disease stage and patient prognosis [4]. Nevertheless, the prognostic information provided by either marker alone is limited. Combining multiple markers within a single index may offer a more comprehensive representation of tumor burden

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and biological behavior. Zhang et al. reported that tumor marker-based indices could improve survival estimation in patients with advanced gastric cancer [5]. In addition, Demir et al. demonstrated the prognostic relevance of an index combining CEA and CA 19-9 in metastatic pancreatic cancer [6]. Collectively, these observations indicate that combined marker models may be useful across gastrointestinal malignancies; however, their role in metastatic gastric cancer has not yet been sufficiently defined.

Therefore, this study aimed to determine whether a tumor marker index derived from CEA and CA 19-9 is associated with survival in patients with metastatic gastric cancer. We also examined the relationship between TMI and established clinicopathological prognostic characteristics.

Materials and methods

This retrospective multicenter study included 400 patients treated for metastatic gastric cancer at six centers in Türkiye between 2013 and 2025. Eligible patients were aged 18 years or older and had histologically confirmed gastric adenocarcinoma with either de novo or recurrent metastatic disease. Patients were excluded if histopathological confirmation was unavailable, baseline CEA or CA 19-9 levels were missing, or their clinical or laboratory records were insufficient for analysis.

Demographic and clinical information was retrospectively obtained from patient files and electronic medical records. The collected variables included age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, tobacco and alcohol use, body mass index, disease presentation, stage at initial diagnosis, previous adjuvant treatment, primary tumor site, metastatic sites, and the number of involved metastatic sites. HER2, microsatellite instability/mismatch repair (MSI/MMR), and programmed death-ligand 1 (PD-L1) results were also recorded when available. Baseline laboratory parameters comprised CEA, CA 19-9, neutrophil, lymphocyte and platelet counts, albumin, and C-reactive protein (CRP). Information regarding the first-line treatment regimen, number of treatment lines administered for metastatic disease, best treatment response, progression, survival status, and follow-up duration was additionally collected.

The neutrophil-to-lymphocyte ratio (NLR) was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count, whereas the platelet-to-lymphocyte ratio (PLR) was derived from the platelet and lymphocyte counts. The prognostic nutritional index (PNI) was calculated as [10 × serum albumin (g/dL)]+[0.005 × total lymphocyte count (/mm^3)]. The C-reactive protein-to-albumin ratio (CAR) was defined as serum CRP divided by serum albumin [7]. The Glasgow Prognostic Score (GPS) was determined from CRP and albumin concentrations. A score of 0 was assigned to patients with CRP≤10 mg/L and albumin ≥3.5 g/dL. Patients with either CRP>10 mg/L or albumin <3.5 g/dL received a score of 1, whereas those meeting both criteria received a score of 2 [8]. Receiver operating characteristic (ROC) curve analyses were used to determine the thresholds for TMI, NLR, PLR, PNI, and CAR before Kaplan-Meier and Cox regression analyses.

Calculation of the tumor marker ındex

The association of TMI with PFS and OS constituted the primary study outcome. PFS was calculated from the date on which metastatic disease was diagnosed to the first evidence of progression or death occurring in the absence of documented progression. For patients who experienced neither event, follow-up was censored on the last date for which clinical information was available. OS represented the time between metastatic diagnosis and death from any cause. Patients who were still alive were censored on the date they were last known to be alive.

The reference upper limits used for CEA and CA 19-9 were 5.0 ng/mL and 37.0 U/mL, respectively. To account for differences in measurement scales, each marker was normalized by dividing its serum concentration by the corresponding upper reference limit. TMI was then calculated as the geometric mean of the normalized CEA and CA 19-9 values, consistent with previously described methods [6, 9].

$$TMI = \sqrt{\frac{CEA(ng/mL)}{5.0} \times \frac{CA19\text{-}9(U/mL)}{37.0}}$$

ROC curve analysis was initially performed to examine the ability of TMI to discriminate patients according to mortality status. The area under the curve was 0.515 (95% CI, 0.417-0.613; P=0.744). The threshold of 0.94, selected by maximizing the Youden index, yielded a sensitivity and specificity of 51.1%. Patients with TMI values below 0.94 were initially classified into the low-TMI group, whereas those with values of 0.94 or higher were classified into the high-TMI group. Given the limited discriminatory performance of this threshold, additional sensitivity analyses were subsequently performed using alternative TMI specifications.

Statistical analysis

IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Continuous variables were reported as mean ± standard deviation or median (range), depending on their distribution, whereas categorical variables were presented as numbers and percentages. The independent-samples t-test was used to compare continuous variables between two independent groups. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test when the assumptions of the chi-square test were not met. The ability of the evaluated indices to classify mortality status was assessed using ROC curve analysis.

To evaluate the robustness of the survival associations, sensitivity analyses were conducted using several alternative TMI specifications: TMI as a continuous variable per one-unit increase, TMI standardized per 1-standard deviation increase, natural log-transformed TMI, the original ROC-derived cut-off of ≥0.94, and the cohort median cut-off of ≥0.944985. Sensitivity analyses were performed separately for OS and PFS. Both unadjusted estimates and estimates obtained from center-stratified, treatment-era-adjusted Cox models were reported.

Kaplan-Meier curves and log-rank tests were used to estimate and compare time-to-event outcomes. Separate multivariable Cox proportional hazards models were constructed for OS and PFS. In the final multivariable models, TMI was included as a continuous variable standardized per 1-standard deviation increase. To account for potential heterogeneity associated with the multicenter design and the long study period, participating center was incorporated as a stratification factor, whereas treatment era was included as an adjustment variable. Hazard ratios were reported with corresponding 95% confidence intervals and *p* values. A two-tailed *p* value of <0.05 was considered statistically significant.

Missingness was assessed separately for each study variable. No missing-data imputation was performed. Descriptive and group-comparison analyses involving variables with missing data were conducted using available cases, with the corresponding denominators reported. Because of the substantial missingness in HER2, PD-L1, and MSI/MMR status, these variables were not included in the primary multivariable Cox regression models. The variables included in the final OS and PFS models had complete data.

Ethical considerations

The research procedures followed the ethical standards of the Declaration of Helsinki and Good Clinical Practice. The study protocol received approval from the Ethics Committee of Alanya Alaaddin Keykubat University Hospital on 23 October 2024 under decision number 23-05.

Results

The study cohort consisted of 400 patients enrolled across six participating centers. The largest proportions were recruited from Manisa Celal Bayar University (MCBÜ; n=174, 43.5%) and Aydın Adnan Menderes University Faculty of Medicine (ADÜ TF; n=153, 38.2%). The distribution of participating centers did not differ significantly between the low- and high-TMI groups (Monte Carlo exact chi-square test, P=0.532). Patients were categorized into three treatment eras: ≤2016 (n=74, 18.5%), 2017-2020 (n=154, 38.5%), and 2021-2025 (n=172, 43.0%). Treatment-era distribution was comparable between the TMI groups (Pearson's chi-square test, P=0.139) (**Table 1**). No missing data were identified for the survival outcomes, TMI, or the clinical and laboratory variables included in the final multivariable models. Missingness was primarily confined to molecular biomarkers. HER2 status was unavailable in

Table 1. Distribution of patients by participating center and treatment era according to TMI groups

Variables	Total, n (%)	Low TMI, n (%)	High TMI, n (%)	*p* value
Participating center				0.532
MCBÜ	174 (43.5)	83 (42.1)	91 (44.8)	
ADÜ TF	153 (38.2)	73 (37.1)	80 (39.4)	
Alanya EAH	26 (6.5)	12 (6.1)	14 (6.9)	
Balıkesir Atatürk City Hospital	24 (6.0)	15 (7.6)	9 (4.4)	
Mardin EAH	13 (3.2)	9 (4.6)	4 (2.0)	
Edirne Sultan 1. Murat State Hospital	10 (2.5)	5 (2.5)	5 (2.5)	
Treatment era				0.139
≤2016	74 (18.5)	42 (21.3)	32 (15.8)	
2017-2020	154 (38.5)	67 (34.0)	87 (42.9)	
2021-2025	172 (43.0)	88 (44.7)	84 (41.4)	
Total	400 (100.0)	197 (100.0)	203 (100.0)	

143 patients (35.8%), PD-L1 status in 331 patients (82.8%), and MSI/MMR status in 305 patients (76.2%). First-line chemotherapy data were missing in 26 patients (6.5%), and the number of metastatic treatment lines was missing in two patients (0.5%). No imputation was performed, and analyses involving variables with missing data were based on available cases (Supplementary Table 1).

Patient age ranged from 25 to 98 years, with a median of 64.0 years. Men accounted for 70.5% of the cohort (n=282), whereas 118 patients (29.5%) were women. An ECOG performance status of 0 or 1 was recorded in 310 patients (77.5%). De novo metastatic disease was present in 286 patients (71.5%). Peritoneal involvement was identified in 47.3% of the cohort, followed by liver involvement in 43.5%. The median follow-up duration was 14.4 months. By the end of follow-up, 391 patients (97.7%) had experienced disease progression and 355 (88.7%) had died (**Table 2**).

Survival analyses

Using the original ROC-derived threshold of 0.94, 197 patients (49.3%) were classified into the low-TMI group and 203 (50.7%) into the high-TMI group. However, the discriminatory performance of this threshold was limited, with an AUC of 0.515 (95% CI, 0.417-0.613; P= 0.744) and a sensitivity and specificity of 51.1%. Age, sex, ECOG performance status, comorbidities, tobacco use, and alcohol use were similarly distributed between the groups (all P>0.05).

Liver involvement was detected in 38.6% of the low-TMI group and 48.3% of the high-TMI group (P=0.049). Bone metastases were also more frequent among patients with high TMI than among those with low TMI (24.6% vs. 12.7%; P=0.002). The frequencies of peritoneal, lung, brain, and other metastases did not differ according to TMI category. PD-L1 results were available for 17.2% of the study population, and PD-L1 expression showed a significant distributional difference between the groups (P=0.010). No association with TMI category was identified for primary tumor location, HER2 status, or MSI status (all P>0.05). The low- and high-TMI groups also showed comparable distributions of the ROC-based NLR, PLR, PNI, and CAR categories (P=0.115, P=0.373, P=0.764, and P=0.385).

First-line chemotherapy selection, best treatment response, number of systemic treatment lines, and immunotherapy use were comparable between the TMI groups (all P>0.05). The objective response rate was 79.7% in the low-TMI group and 73.9% in the high-TMI group (P=0.170). Disease control was achieved in 80.7% and 75.4% of the two groups (P=0.197) (**Table 3**).

In the entire patient cohort, the median OS was 14.73 months (95% CI: 13.19-16.27), and the median PFS was 12.00 months (95% CI: 10.69-13.30). No significant differences were observed in either OS or PFS with respect to age, sex, tobacco and alcohol use, comorbidities, BMI, tumor location, or HER2 status (all P>0.05). Although no significant difference was

Table 2. Comparison of sociodemographic and clinical characteristics according to TMI groups

Variables	Total N=400	Low TMI N=197	High TMI N=203	p
Age				0.618
Mean±SD	62.78±11.59	63.11±12.37	62.34±10.80	
Median (min-max)	64.0 (25-98)	65.5 (25-87)	63.1 (33-98)	
Age group				0.166
<65	211 (52.8)	97 (49.2)	114 (56.2)	
≥65	189 (47.2)	100 (50.8)	89 (43.8)	
Sex				0.284
Female	118 (29.5)	63 (32.0)	55 (27.1)	
Male	282 (70.5)	134 (68.0)	148 (72.9)	
ECOG performance status				0.484
0	120 (30.0)	57 (28.9)	63 (31.0)	
1	190 (47.5)	89 (45.2)	101 (49.8)	
2	77 (19.3)	43 (21.8)	34 (16.7)	
3	13 (3.3)	8 (4.1)	5 (2.5)	
BMI				0.339
<25	267 (66.8)	136 (69.0)	131 (64.5)	
≥25	133 (33.3)	61 (31.0)	72 (35.5)	
Disease status				0.800
De-novo metastatic	286 (71.5)	142 (72.1)	144 (70.9)	
Recurrent metastatic	114 (28.5)	55 (27.9)	59 (29.1)	
Adjuvant chemotherapy history				0.527
No	278 (69.5)	134 (68.0)	144 (70.9)	
Yes	122 (30.5)	63 (32.0)	59 (29.1)	
Stage at diagnosis				0.832
Stage I	3 (0.8)	2 (1.0)	1 (0.5)	
Stage II	28 (7.0)	12 (6.1)	16 (7.9)	
Stage III	91 (22.8)	46 (23.4)	45 (22.2)	
Stage IV	278 (69.4)	137 (69.5)	141 (69.5)	
Liver metastasis				0.049
No	226 (56.5)	121 (61.4)	105 (51.7)	
Yes	174 (43.5)	76 (38.6)	98 (48.3)	
Peritoneal metastasis				0.537
No	211 (52.8)	107 (54.3)	104 (51.2)	
Yes	189 (47.3)	90 (45.7)	99 (48.8)	
Lung metastasis				0.161
No	320 (80.0)	152 (77.2)	168 (82.8)	
Yes	80 (20.0)	45 (22.8)	35 (17.2)	
Brain metastasis				0.681
No	395 (98.8)	194 (98.5)	201 (99.0)	
Yes	5 (1.2)	3 (1.5)	2 (1.0)	
Bone metastasis				0.002
No	325 (81.3)	172 (87.3)	153 (75.4)	
Yes	75 (18.7)	25 (12.7)	50 (24.6)	
Other metastases				0.934
No	147 (36.8)	72 (36.5)	75 (36.9)	
Yes	253 (63.2)	125 (63.5)	128 (63.1)	

Number of metastatic sites				0.150
1	138 (34.5)	69 (35.0)	69 (34.0)	
2	138 (34.5)	74 (37.6)	64 (31.5)	
3	84 (21.0)	40 (20.3)	44 (21.7)	
4	29 (7.2)	8 (4.1)	21 (10.3)	
5	11 (2.8)	6 (3.0)	5 (2.5)	
Tumor location				0.503
Cardia	98 (24.4)	42 (21.3)	56 (27.6)	
Corpus	151 (37.8)	76 (38.6)	75 (36.9)	
Fundus	16 (4.0)	9 (4.6)	7 (3.4)	
Antrum	135 (33.8)	70 (35.5)	65 (32.0)	
HER2*				0.945
Wild-type/negative	210 (81.7)	95 (81.9)	115 (81.6)	
Positive	47 (18.3)	21 (18.1)	26 (18.4)	
MSI status*				0.054
MSS/Pmmr	88 (92.6)	40 (87.0)	48 (98.0)	
MSI-H/dMMR	7 (7.4)	6 (13.0)	1 (2.0)	
PDL-1 expression*				0.010
0	43 (62.3)	20 (58.8)	23 (65.7)	
1-50	19 (27.5)	7 (20.6)	12 (34.3)	
>50	7 (10.2)	7 (20.6)	0 (0.0)	
Follow-up time (months)				0.117
Median (min-max)	14.4 (0.1-190.7)	16.3 (0.47-190.7)	12.9 (0.1-155.8)	

Abbreviations: TMI, tumor marker index; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; MSI, microsatellite instability; MSS, microsatellite stable; pMMR, proficient mismatch repair; dMMR, deficient mismatch repair; PD-L1, programmed death-ligand 1; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. *Among patients with available HER2, PD-L1, and MSI data.

Table 3. Comparison of treatment response according to TMI groups

Variables	Low TMI (N=197)	High TMI (N=203)	P
ORR			
SD+PD	40 (20.3)	53 (26.1)	0.170
CR+PR	157 (79.7)	150 (73.9)	
DCR			
PD	38 (19.3)	50 (24.6)	0.197
CR+PR+SD	159 (80.7)	153 (75.4)	

TMI, tumor marker index; ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. *p* values were calculated using the Pearson chi-square test.

observed with respect to ECOG performance status, a trend toward shorter survival times was observed as the ECOG score increased.

Disease status had a significant effect on survival. In patients with recurrent metastatic disease, both OS and PFS (29.80 months vs. 10.90 months; 25.43 months vs. 8.26 months, respectively; P<0.001) were significantly longer than in patients with de novo metastatic disease. Similarly, OS (26.30 months vs. 11.40 months; P<0.001) and PFS (22.46 months vs. 8.23 months; P<0.001) were longer in patients with a history of adjuvant chemotherapy. Stage at diagnosis was significantly associated with both OS and PFS (P<0.001). When evaluated in terms of metastatic involvement, OS was significantly shorter in patients with liver and bone metastases (P=0.022 and P<0.001, respectively). As the number of metastatic sites increased, both OS (P=0.002) and PFS (P=0.001) decreased significantly. In contrast, no significant differences in survival outcomes were observed for peritoneal, lung, or brain metastases (P>0.05) (**Table 4**).

When treatment-related factors were examined, a statistically significant difference in survival was observed among first-line chemotherapy regimens (P=0.008). The longest median OS was observed in the XELOX (17.66

Table 4. Kaplan-Meier survival analyses for OS and PFS according to clinicopathological variables

Variables	OS median, months (95% CI)	P	PFS median, months (95% CI)	P
Overall	14.73 (13.19-16.27)	-	12.00 (10.69-13.30)	-
Age				
<65	15.30 (13.75-16.84)	0.768	13.06 (11.44-14.68)	0.482
≥65	14.10 (11.34-16.85)		11.40 (9.62-13.17)	
Sex				
Female	16.00 (13.25-18.75)	0.762	11.16 (8.49-13.84)	0.712
Male	14.36 (12.79-15.93)		12.36 (10.51-14.22)	
ECOG performance status				
0	14.16 (11.31-17.01)	0.130	13.23 (11.22-15.24)	0.095
1	15.56 (13.71-17.42)		12.70 (11.19-14.20)	
2	15.90 (10.57-21.22)		7.90 (4.27-11.52)	
3	5.16 (0.51-9.82)		4.70 (2.54-6.85)	
BMI				
<25	15.56 (13.69-17.44)	0.278	12.06 (10.62-13.50)	0.447
≥25	14.06 (11.15-16.97)		11.90 (8.91-14.88)	
Disease status				
De-novo metastatic	10.90 (9.51-12.28)	<0.001	8.26 (7.11-9.42)	<0.001
Recurrent metastatic	29.80 (26.64-32.95)		25.43 (21.59-29.27)	
Adjuvant chemotherapy history				
No	11.40 (9.64-13.16)	<0.001	8.23 (6.39-9.52)	<0.001
Yes	26.30 (22.79-29.81)		22.46 (18.98-25.94)	
Stage at diagnosis				
Stage I	40.03 (0.00-92.41)	<0.001	40.03 (0.00-96.57)	<0.001
Stage II	43.16 (10.48-75.85)		22.96 (12.68-33.25)	
Stage III	27.13 (23.16-31.10)		24.80 (20.55-29.04)	
Stage IV	10.63 (9.04-12.22)		8.13 (7.25-9.01)	
Liver metastasis				
No	15.90 (14.16-17.63)	0.022	13.36 (11.81-14.91)	0.129
Yes	12.83 (10.88-14.78)		10.73 (8.99-12.46)	
Peritoneal metastasis				
No	15.93 (13.14-18.72)	0.146	11.80 (9.84-13.75)	0.829
Yes	14.16 (12.60-15.73)		12.70 (10.54-14.85)	
Lung metastasis				
No	14.73 (13.04-16.42)	0.927	12.33 (10.80-13.66)	0.728
Yes	14.86 (12.43-17.30)		11.63 (8.99-14.27)	
Brain metastasis				
No	14.83 (13.27-16.39)	0.168	12.06 (10.72-13.41)	0.406
Yes	11.90 (0.00-27.07)		11.90 (0.00-27.07)	
Bone metastasis				
No	16.00 (14.27-17.72)	<0.001	13.06 (11.79-14.33)	<0.001
Yes	8.80 (5.09-12.50)		7.50 (5.71-9.29)	
Number of metastatic sites				
1	17.70 (15.42-19.97)	0.002	14.66 (12.36-17.01)	0.001
2	13.23 (10.61-15.85)		9.40 (6.25-12.55)	
3	14.10 (12.64-15.55)		12.06 (9.89-14.23)	
4	11.26 (7.16-15.36)		8.70 (1.72-15.67)	
5	11.90 (0.17-23.62)		11.90 (3.10-20.69)	

HER2 status				
Wild-type/negative	15.56 (13.63-17.50)	0.488	12.06 (10.51-13.62)	0.753
Mutant/positive	14.36 (11.17-17.56)		8.53 (5.82-11.24)	
First-line chemotherapy regimen				
FOLFOX	17.36 (8.63-26.10)	0.008	10.76 (6.62-14.90)	0.334
XELOX/CAPOX	17.66 (15.21-20.11)		15.30 (12.36-18.24)	
Mdcf	16.10 (12.50-19.69)		14.46 (11.43-17.49)	
CF	7.36 (5.41-9.32)		7.36 (5.41-9.32)	
FOLFIRI	16.00 (0.00-45.09)		11.46 (0.00-26.39)	
Capecitabine	10.76 (5.34-16.19)		8.63 (0.00-18.08)	
Chemotherapy+trastuzumab	14.23 (7.26-23.20)		10.33 (2.33-18.33)	
Other	14.06 (9.30-18.82)		8.13 (3.46-12.80)	
Number of metastatic treatment lines				
1 line	13.06 (11.44-14.68)	0.001	13.06 (11.67-14.45)	0.022
2 lines	21.43 (11.21-31.65)		9.63 (7.85-11.41)	
3 lines	18.10 (10.14-26.05)		7.90 (5.41-10.38)	
≥4 lines	26.06 (12.82-39.30)		8.23 (0.00-16.53)	

OS, overall survival; PFS, progression-free survival; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin; XELOX/CAPOX, capecitabine and oxaliplatin; mDCF, modified docetaxel, cisplatin, and 5-fluorouracil; CF, cisplatin and 5-fluorouracil; FOLFIRI, leucovorin, 5-fluorouracil, and irinotecan. *p* values were calculated using the log-rank test.

months), FOLFOX (17.36 months), and mDCF (16.10 months) regimens, whereas median OS was significantly lower in patients treated with the CF regimen (7.36 months). In contrast, no significant difference in PFS was observed among first-line chemotherapy regimens (P= 0.334). The number of chemotherapy lines received in metastatic disease was significantly associated with both OS (P=0.001) and PFS (P=0.022). In addition, the GPS score was found to be significantly associated with PFS (P=0.004) (**Table 4**).

Among the inflammatory markers, NLR was found to be significantly associated with both OS and PFS. In patients with an NLR≥3.1, median OS was shorter than in those with an NLR<3.1 (11.26 months vs. 19.90 months; P<0.001). Similarly, median PFS was also lower in the NLR≥3.1 group (8.56 months vs. 16.00 months; P<0.001). The CAR value was also associated with both OS and PFS. In patients with a CAR≥2.0, median OS (16.50 months vs. 12.53 months; P=0.012) and median PFS (13.66 months vs. 9.46 months; P=0.022) were longer. In contrast, no significant differences in OS or PFS were observed with respect to PLR and PNI (P>0.05) (**Table 5**).

Using the original ≥0.94 threshold, patients in the high-TMI group had shorter median OS than those in the low-TMI group (13.06 vs. 16.43 months; log-rank P=0.048). Median PFS was also shorter in the high-TMI group (10.53 vs. 14.06 months; log-rank P=0.011) (**Figures 1** and **2**).

Sensitivity analyses demonstrated that the association between TMI and survival varied according to how TMI was modeled. In the center-stratified, treatment-era-adjusted analyses, continuous TMI was not significantly associated with OS (HR per one-unit increase = 0.993, 95% CI: 0.985-1.002; P=0.124) or PFS (HR= 0.994, 95% CI: 0.986-1.003; P=0.170). Similarly, neither TMI standardized per 1-SD increase nor natural log-transformed TMI was significantly associated with OS or PFS. In contrast, the categorical ≥0.94 definition was associated with OS (HR=1.303, 95% CI: 1.039-1.632; P=0.022) and PFS (HR=1.511, 95% CI: 1.210-1.886; P<0.001). The median-based threshold produced similar estimates; however, the cohort median of 0.944985 was nearly identical to the original ROC-derived threshold. These findings indicate that the observed association was dependent on dichotomization around 0.94 rather than representing a consistent continuous relationship.

In the final center-stratified, treatment-era-adjusted multivariable Cox model for OS, recur-

Table 5. Association of inflammatory and nutritional indices with overall survival and progression-free survival

Variables	Median OS, months (95% CI)	*p* value	Median PFS, months (95% CI)	*p* value
NLR				
<3.1	19.90 (16.61-23.18)	<0.001	16.00 (13.67-18.33)	<0.001
≥3.1	11.26 (9.43-13.09)		8.56 (6.78-10.34)	
PLR				
<3.1	15.90 (13.71-18.08)	0.966	14.46 (12.56-16.37)	0.206
≥3.1	14.10 (12.03-16.16)		9.73 (7.90-11.56)	
PNI				
<7.0	14.83 (12.82-16.84)	0.681	14.16 (12.40-15.92)	0.493
≥7.0	14.46 (12.17-16.75)		10.33 (8.60-12.06)	
CAR				
<2.0	12.53 (10.22-14.83)	0.012	9.46 (6.58-12.34)	0.022
≥2.0	16.50 (14.59-18.40)		13.66 (11.17-16.10)	
GPS				
0	17.60 (10.61-24.59)	0.141	11.83 (8.17-15.48)	0.004
1	12.53 (10.24-14.82)		9.46 (7.84-11.09)	
2	15.86 (14.30-17.42)		14.10 (11.92-16.27)	

OS, overall survival; PFS, progression-free survival; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; CAR, C-reactive protein-to-albumin ratio; GPS, Glasgow Prognostic Score.

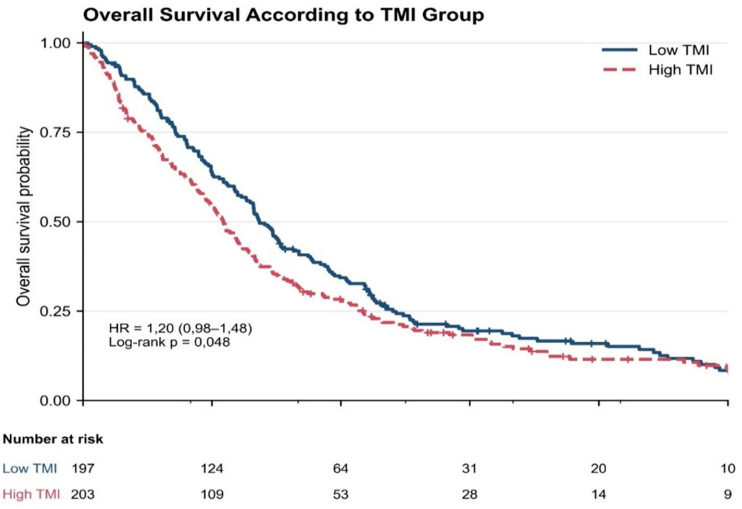

Figure 1. Kaplan-Meier overall survival curves according to TMI groups.

rent metastatic disease was associated with a lower risk of mortality than de novo metastatic disease (HR=0.361, 95% CI: 0.272-0.480; P<0.001). Liver metastasis (HR=1.331, 95% CI: 1.051-1.685; P=0.018), bone metastasis (HR=1.689, 95% CI: 1.223-2.334; P=0.001), and NLR≥3.1 (HR=1.682, 95% CI: 1.345-2.104; P<0.001) were independently associated with a higher risk of mortality. CAR≥2.0 was associated with a lower risk of mortality (HR=0.562, 95% CI: 0.441-0.715; P<0.001). TMI, evaluated per 1-SD increase, was not independently associated with OS (HR=0.920, 95% CI: 0.828-1.023; P=0.124) Similarly, in the final center-stratified, treatment-era-adjusted multivariable Cox model for PFS, TMI per 1-SD increase was not independently associated with progression or death (HR=0.930, 95% CI: 0.838-1.032; P=0.170). Recurrent metastatic disease was associated with a lower risk of progression or death, whereas liver metastasis, bone metastasis, NLR≥3.1, and the 2021-2025 treatment era were associated with higher risks. CAR≥2.0 was associated with a lower risk of progression or death (**Table 6**).

Discussion

This multicenter real-world analysis included 400 patients with metastatic gastric cancer and examined the relationship of TMI with clinicopathological characteristics and survival outcomes. In the categorical analyses, TMI≥0.94 was associated with shorter OS and PFS. However, when TMI was evaluated as a continuous variable standardized per 1-SD increase, it was not independently associated with either OS or PFS in the final multivariable models. Therefore, the observed association should be interpreted as threshold-dependent and exploratory rather than evidence that TMI is an independent prognostic factor. The fact that the majority of patients in our cohort had de novo metastases, the high prevalence of peritoneal and liver metastases, and the high rates of progression and mortality during follow-up reflect the aggressive course of metastatic gastric cancer. According to the

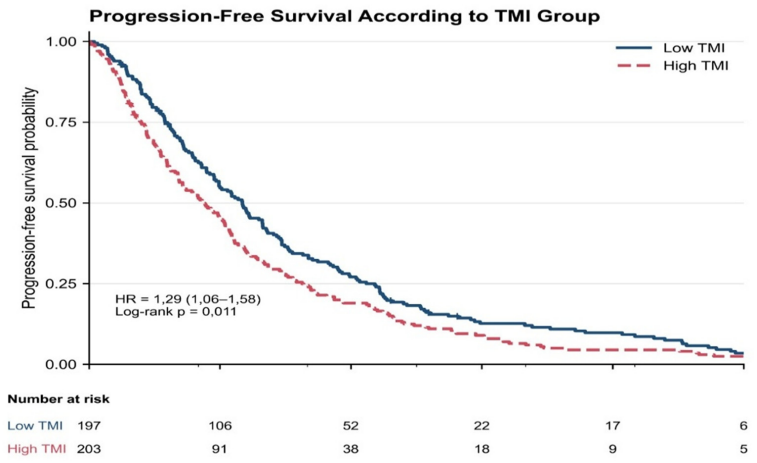

Figure 2. Kaplan-Meier progression-free survival curves according to TMI groups.

literature, survival in metastatic gastric cancer is influenced by numerous clinical and biological factors, including performance status, the number of metastatic sites, peritoneal and visceral organ involvement, tumor biology, inflammatory and nutritional status, and treatment response. Although the majority of patients in our study had good performance status at baseline, the high rate of de novo metastatic disease and the significant burden of peritoneal and visceral metastases can be considered key features explaining the poor prognosis in this patient group.

In a retrospective analysis presented at ASCO GI 2024, it was reported that patients with de novo metastatic disease had a higher number of metastatic sites and worse OS and PFS outcomes compared to patients with recurrent metastatic disease [10]. Consistent with the literature, our study also found that recurrent metastatic disease was associated with a lower risk of mortality compared to de novo metastatic disease. The fact that 71.5% of patients in our cohort had de novo metastatic disease suggests that the study population had a high metastatic burden, which may be a significant factor partially explaining the high rates of progression and mortality observed. Another factor commonly observed in metastatic gastric cancer and associated with a poor prognosis in the literature is peritoneal metastasis [11]. Although peritoneal metastasis was the most frequently detected metastasis in our study, it did not demonstrate a significant prognostic effect in survival analyses, and no significant difference was observed between the low- and high-TMI groups. The fact that peritoneal metastasis was not found to be associated with survival in our study may be related to the lack of analysis of details such as the peritoneal disease burden, the presence of ascites, or the extent of radiological spread.

It is noteworthy that liver and bone metastases were observed significantly more frequently in the high TMI group. While liver metastasis is an important metastatic pattern in metastatic gastric cancer that reflects the visceral disease burden and hematogenous spread, bone metastasis is observed less frequently and is generally associated with more aggressive systemic disease and a poor clinical course. In prognostic modeling studies conducted in patients with metastatic gastric cancer, both liver metastases and bone metastases have been reported as independent poor prognostic factors for overall survival [12]. In the final multivariable OS model, both liver and bone metastases were independently associated with higher mortality. Liver metastasis was associated with a 33.1% increase in the risk of mortality (HR=1.331, 95% CI: 1.051-1.685; P=0.018), whereas bone metastasis was associated with a 68.9% increase (HR=1.689, 95% CI: 1.223-2.334; P=0.001). Both metastatic sites were also independently associated with a higher risk of progression or death in the PFS model. The greater frequency of liver and bone metastases in the high-TMI group may partly explain the survival differences observed in the categorical TMI analyses.

The absence of significant differences between the low- and high-TMI groups in treatment characteristics is relevant to the interpretation of our findings. First-line chemotherapy regimens, the number of metastatic treatment lines, objective response rates, and disease control rates were comparable between the groups. However, this observation alone does not establish that the survival difference was independent of treatment-related factors. Although

Table 6. Multivariable Cox regression analysis for progression-free survival and overall survival

Variables	Overall Survival (OS) HR (95% CI)	P	Progression-Free Survival (PFS) HR (95% CI)	P
Age, per 10-year increase	0.967 (0.876-1.068)	0.513	0.933 (0.843-1.031)	0.173
Male sex (ref: female)	1.108 (0.866-1.418)	0.415	1.050 (0.830-1.328)	0.683
ECOG performance status, per 1-point increase	0.921 (0.776-1.093)	0.345	1.019 (0.866-1.198)	0.820
Recurrent metastatic disease (ref: de novo)	0.361 (0.272-0.480)	<0.001	0.278 (0.210-0.369)	<0.001
Liver metastasis (ref: absent)	1.331 (1.051-1.685)	0.018	1.393 (1.107-1.752)	0.005
Bone metastasis (ref: absent)	1.689 (1.223-2.334)	0.001	1.860 (1.350-2.563)	<0.001
Number of metastatic sites, per additional site	1.044 (0.915-1.192)	0.522	0.969 (0.856-1.097)	0.620
NLR ≥3.1 (ref: <3.1)	1.682 (1.345-2.104)	<0.001	1.583 (1.279-1.960)	<0.001
CAR ≥2.0 (ref: <2.0)	0.562 (0.441-0.715)	<0.001	0.575 (0.456-0.725)	<0.001
Treatment era				
≤2016	Ref	-	Ref	-
2017-2020	1.378 (0.999-1.900)	0.051	1.383 (1.000-1.913)	0.050
2021-2025	1.787 (1.239-2.577)	0.002	2.255 (1.568-3.244)	<0.001
TMI, per 1-SD increase	0.920 (0.828-1.023)	0.124	0.930 (0.838-1.032)	0.170

Abbreviations: OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; NLR, neutrophil-to-lymphocyte ratio; CAR, C-reactive protein-to-albumin ratio; TMI, tumor marker index; SD, standard deviation. Participating center was incorporated as a stratification factor, and treatment era was included using two indicator variables. TMI was evaluated per 1-standard deviation increase. A two-tailed *p* value of <0.05 was considered statistically significant.

categorical TMI was not associated with initial treatment response, its relationship with the subsequent disease course remains exploratory.

Systemic inflammation and impaired nutritional status are closely linked to cancer progression and patient outcomes [13, 14]. Indices derived from routine laboratory measurements, including NLR, PLR, PNI, CAR, and GPS, may provide information on the host inflammatory response, nutritional reserve, and overall disease burden. A real-world analysis of metastatic gastric cancer associated an elevated modified GPS with unfavorable OS [15]. A systematic review and meta-analysis also supported the prognostic relevance of NLR and PLR for OS and PFS in gastric cancer [16]. In our cohort, an NLR of ≥3.1 was associated with shorter OS and PFS. This relationship persisted after multivariable adjustment, with elevated NLR independently increasing both mortality and progression risks. Conversely, PLR, PNI, and GPS were not significantly related to survival. Differences in patient populations, treatment exposure, laboratory sampling time, and threshold selection may account for the variable prognostic performance of these indices across studies.

In a meta-analysis examining the association between CAR - which simultaneously reflects systemic inflammation and nutritional status through the combined assessment of CRP and albumin - and gastric cancer, a high CAR was shown to be a predictor of poor overall survival and progression-free survival [17]. However, in our study, both OS and PFS were found to be longer in patients with a CAR≥2.0, and multivariate analyses revealed that a high CAR was associated with lower mortality and a lower risk of progression. It is thought that this discrepancy may be related to factors such as the retrospective and multicenter nature of our study, heterogeneity in CRP and albumin measurements, the inability to rule out associations with infection or acute inflammatory conditions, albumin replacement, nutritional supplements, or the choice of cutoff values. In our study, no significant differences were found between the low and high TMI groups in terms of NLR, PLR, PNI, GPS, and CAR values. This suggests that this index is not merely an indirect reflection of systemic inflammation or nutritional status.

In the primary categorical analysis, median OS and PFS were significantly shorter in patients with TMI≥0.94 than in those with TMI<0.94. However, the additional sensitivity analyses showed that the association varied according to how TMI was modeled. TMI was not significantly associated with OS or PFS when evaluated as a continuous variable, per 1-SD increase, or after natural log transformation. In contrast, significant associations were observed when TMI was dichotomized at approximately 0.94. These findings suggest that the

observed prognostic separation is threshold-dependent and should not be interpreted as evidence of a robust continuous prognostic relationship. Therefore, the ≥0.94 finding should be regarded as exploratory and requires validation in an independent cohort before clinical application.

Similarly, the prognostic value of the TMI - which evaluates CEA and CA 19-9 together - has also been demonstrated in various types of gastrointestinal malignancies. İlhan and colleagues demonstrated that a new tumor marker index based on CEA and CA 19-9 could be used as a prognostic factor in metastatic colorectal cancer [9], while Demir and colleagues showed that a combined tumor marker index could be valuable in predicting prognosis in metastatic pancreatic cancer [6]. In the present study, dichotomization of TMI at approximately 0.94 identified groups with different survival outcomes. However, unlike a consistently demonstrable continuous association, this relationship was dependent on the selected threshold. Therefore, our findings should be considered hypothesis-generating and cannot yet establish TMI as a clinically applicable prognostic tool in metastatic gastric cance.

Limitations

The retrospective design of our study is its most significant limitation. The combined evaluation of patients with de novo and recurrent metastatic disease, the fact that patients with recurrent metastatic disease received different treatments during the adjuvant phase, and the possibility that patients with de novo metastatic disease may have had a more extensive disease burden may have led to heterogeneity in the study population. Despite normalization of CEA and CA 19-9 values to their respective upper limits of normal and adjustment for treatment era and participating center, residual heterogeneity related to changes in laboratory assays, treatment strategies, and HER2 and PD-L1 testing practices over the long study period cannot be fully excluded.

Furthermore, no externally validated TMI cut-off is currently available for metastatic gastric cancer. The original threshold of 0.94 was derived from the present cohort and demonstrated poor discriminatory performance, with an AUC of 0.515 and sensitivity and specificity of 51.1%. Although categorical analyses around this threshold showed significant survival associations, continuous and log-transformed TMI did not. The observed relationship was therefore sensitive to model specification and may partly reflect data-dependent dichotomization. External validation in an independent cohort is required before any TMI threshold can be considered for clinical use.

The high rates of missing HER2, PD-L1, and MSI/MMR data reflect changes in molecular testing practices over the long study period and limited the ability to evaluate their prognostic effects. Although these variables were excluded from the primary multivariable models to avoid a substantial reduction in sample size, their absence may have resulted in residual confounding and selection bias.

Conclusion

In conclusion, the CEA- and CA 19-9-based TMI was associated with OS and PFS when dichotomized at approximately 0.94. However, TMI was not independently associated with either outcome when evaluated as a continuous variable in the final multivariable Cox models. The observed prognostic association therefore appears to be threshold-dependent and should be interpreted as exploratory. External validation in independent cohorts is required before TMI can be considered for routine prognostic risk stratification in metastatic gastric cancer.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Summary of missing data for key variables

Variable	Available, n	Available, %	Missing, n	Missing, %
Overall survival (OS) time	400	100.0	0	0.0
OS event status	400	100.0	0	0.0
Progression-free survival (PFS) time	400	100.0	0	0.0
PFS event status	400	100.0	0	0.0
Tumor marker index (TMI)	400	100.0	0	0.0
CEA	400	100.0	0	0.0
CA 19-9	400	100.0	0	0.0
Participating center	400	100.0	0	0.0
Year of diagnosis	400	100.0	0	0.0
HER2 status	257	64.2	143	35.8
PD-L1 status	69	17.2	331	82.8
MSI/MMR status	95	23.8	305	76.2
C-reactive protein (CRP)	400	100.0	0	0.0
Albumin	400	100.0	0	0.0
Neutrophil-to-lymphocyte ratio (NLR)	400	100.0	0	0.0
Platelet-to-lymphocyte ratio (PLR)	400	100.0	0	0.0
Prognostic nutritional index (PNI)	400	100.0	0	0.0
C-reactive protein-to-albumin ratio (CAR)	400	100.0	0	0.0
Glasgow prognostic score (GPS)	400	100.0	0	0.0
Age	400	100.0	0	0.0
Sex	400	100.0	0	0.0
ECOG performance status	400	100.0	0	0.0
Disease status (de novo/recurrent)	400	100.0	0	0.0
Liver metastasis	400	100.0	0	0.0
Bone metastasis	400	100.0	0	0.0
Number of metastatic sites	400	100.0	0	0.0
First-line chemotherapy regimen	374	93.5	26	6.5
Number of metastatic treatment lines	398	99.5	2	0.5