DOI: 10.14744/ejmi.2612618
EJMI 2026;10(4):618–627

Research Article

Combined Assessment of CEA and Systemic Immune-Inflammation Index in Metastatic Colorectal Cancer: A Single-Center Retrospective Study

Nadide Demirel Aydın

Department of Medical Oncology, Zonguldak Atatürk State Hospital, Zonguldak, Türkiye

Abstract

Objectives: To evaluate the prognostic significance of CEA and SII and their combined assessment in metastatic colorectal cancer (mCRC).

Methods: This retrospective single-center study included 80 patients with mCRC treated at our institution between January 2021 and December 2025. CEA and hematological parameters for SII were obtained from medical records. Cutoff values were determined by receiver operating characteristic analysis. Patients were classified into low- and high-level groups, and a three-tier classification was established according to combined CEA-SII status. OS and PFS were analyzed using Kaplan-Meier and Cox regression analyses.

Results: Cutoff values for OS were 4.65 ng/mL for CEA and 826.1 for SII. Elevated CEA was associated with shorter OS and PFS. In multivariate analysis, elevated CEA independently predicted poor OS (HR, 3.676; 95% CI, 1.435-9.418; p=0.007). SII alone was not independently prognostic. However, the combined CEA-SII group independently predicted OS, with each increase in risk category associated with a 77.5% higher risk of death (HR, 1.775; 95% CI, 1.171-2.689; p=0.007). The combined group was associated with PFS in univariate but not multivariate analysis.

Conclusion: Elevated CEA independently predicts OS in mCRC, whereas SII alone does not. CEA-SII assessment provides additional prognostic information for OS and may facilitate risk stratification.

Keywords: Biomarker, carcinoembryonic antigen, metastatic colorectal cancer, overall survival, prognosis, systemic immune-inflammation index

Cite This Article: *Demirel Aydın N. Combined Assessment of CEA and Systemic Immune-Inflammation Index in Metastatic Colorectal Cancer: A Single-Center Retrospective Study. EJMI 2026;10(4):618–627.*

Colorectal cancer (CRC) remains a major global health problem and continues to rank among the leading causes of cancer incidence and cancer-related mortality despite substantial advances in screening programs, diagnostic techniques, and therapeutic options.[1] Although treatment strategies for mCRC have evolved considerably over the last decade, survival outcomes remain unsatisfactory for many patients.[2] Therefore, identifying readily available and cost-effective biomarkers that can accurately predict prognosis is of considerable clinical importance.

Accumulating evidence indicates that systemic inflammation plays a pivotal role in cancer development and progression. Inflammatory pathways influence multiple biological processes involved in tumor growth, including proliferation, angiogenesis, invasion, and metastatic dissemination.[3,4] Accordingly, several hematological inflammatory markers obtained from routinely available laboratory parameters have been evaluated as prognostic biomarkers across

Address for correspondence: Nadide Demirel Aydın, MD. Department of Medical Oncology, Zonguldak Atatürk State Hospital, Zonguldak, Türkiye
Phone: +90 542 788 19 50 **E-mail:** nadide_demirel@hotmail.com

Submitted Date: July 9, 2026 **Revised Date:** September 15, 2026 **Accepted Date:** September 15, 2026

©Copyright 2026 by Eurasian Journal of Medical Investigation - Available online at www.ejmi.org
OPEN ACCESS This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

different malignancies.[5] Elevated SII values have consistently been linked to adverse clinical outcomes in a variety of solid tumors.[4,6]

CEA continues to be the most frequently used serum biomarker in colorectal cancer. Increased baseline CEA concentrations have been associated with greater tumor burden, therapeutic response, and disease progression, and numerous studies have demonstrated their association with inferior survival outcomes.[7–9] However, while CEA primarily reflects tumor biology, it provides limited information regarding the host inflammatory response.

Recent evidence suggests that combining tumor-specific biomarkers with inflammation-based indices may improve prognostic stratification.[10] Since CEA reflects tumor burden whereas SII represents host inflammatory status, combining these two biomarkers may provide a broader assessment of tumor-host interactions than either marker alone. However, evidence regarding the prognostic utility of this combined approach in patients with metastatic colorectal cancer remains limited.

The present study was designed to examine the prognostic relevance of baseline CEA and SII in patients with metastatic colorectal cancer. In addition, we investigated whether integrating these two readily available biomarkers into a single classification system could provide more accurate prognostic stratification for overall survival and progression-free survival than either marker alone.

Materials and Methods

Study Design and Patients

This retrospective observational study included patients with mCRC who were treated at the Department of Medical Oncology, Zonguldak Atatürk State Hospital, between January 2021 and December 2025. Patients were considered eligible if baseline serum CEA measurements and complete blood count data obtained at the time of metastatic disease diagnosis were available. The study population included patients with either de novo or recurrent metastatic colorectal cancer who received first-line systemic treatment for metastatic disease. Patients with incomplete clinical or laboratory data, active infection, active inflammatory or autoimmune disease, hematological disorders, systemic corticosteroid use, or recent surgery at the time of baseline assessment were excluded. Clinical information, including demographic characteristics, tumor features, metastatic involvement, laboratory parameters, treatment details, and survival data, was retrospectively retrieved from the hospital's electronic medical record system. For this study, metastatic burden was classified according to the number of metastatic organs involved. A study-specific classification was used, with oligometastatic disease defined as involvement of ≤3 metastatic organs and multiple metastatic disease defined as involvement of ≥4 metastatic organs.

Baseline counts of platelets, neutrophils, and lymphocytes were obtained from routine complete blood count tests performed at the diagnosis of metastatic disease. The SII was calculated as the platelet count multiplied by the neutrophil count and divided by the lymphocyte count. Baseline CEA levels were also recorded for all patients. Optimal cutoff points for CEA and SII were identified through ROC curve analysis, and patients were categorized into low- and high-level groups based on these thresholds. To assess the prognostic value of combining these biomarkers, patients were further classified into three risk groups according to their baseline CEA and SII status. Since the combined classification was derived from the individual CEA and SII variables, two separate multivariable Cox regression models were used to avoid potential multicollinearity.

OS and PFS constituted the primary endpoints of the study. PFS was calculated from the diagnosis of metastatic disease until documented radiological or clinical progression, death, or the most recent follow-up, whichever came earliest. OS was determined from the date of metastatic diagnosis to death or, for patients who remained alive, to the most recent follow-up date.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean±standard deviation or median (minimum–maximum), as appropriate according to their distribution, while categorical variables were expressed as numbers and percentages. Receiver operating characteristic (ROC) analysis was used to establish optimal cutoff points for CEA and SII. Survival distributions were analyzed by the Kaplan–Meier method, with between-group differences assessed using the log-rank test. Associations of clinical variables with OS and PFS were initially examined through univariable Cox proportional hazards regression. Variables with $p<0.10$ in the univariable analysis were included in the multivariable models. To account for potential multicollinearity arising from the derivation of the combined CEA–SII classification from the individual CEA and SII groups, two separate multivariable Cox regression models were constructed. All tests were two-sided, and $p<0.05$ was considered statistically significant.

Ethics Approval

Ethical approval for this study was granted by the Zonguldak Bülent Ecevit University Non-Interventional Clinical Research Ethics Committee (no: 2026/10, date: 20.05.2026).

The study was conducted in compliance with the ethical standards of the Declaration of Helsinki.

Results

The analysis included 80 patients diagnosed with mCRC. Baseline demographic, clinical, and laboratory features of the cohort are summarized in Table 1.

Table 1. Baseline demographic, clinical, laboratory, and treatment characteristics

Variable	Category / Value	n (%) or Mean±SD	Median (Min-Max)
Demographic Characteristics			
Age (years)		62.39±11.01	64.00 (25-81)
Sex	Female	29 (36.3)	
	Male	51 (63.7)	
Tumor Characteristics			
ECOG Performance Status	0	70 (87.5)	
	1	10 (12.5)	
Tumor Location	Right colon	22 (27.5)	
	Left colon	26 (32.5)	
	Rectum	32 (40.0)	
Grade	Grade 2	63 (78.8)	
	Grade 3	17 (21.2)	
Metastasis Characteristics			
Liver Metastasis	No	36 (45.0)	
	Yes	44 (55.0)	
Lung Metastasis	No	62 (77.5)	
	Yes	18 (22.5)	
Peritoneal Metastasis	No	75 (93.8)	
	Yes	5 (6.3)	
Metastatic Burden	Oligometastatic (≤3 organs)	24 (30.0)	
	Multiple metastatic disease (≥4 organs)	56 (70.0)	
Other Metastasis	No	59 (73.8)	
	Yes	21 (26.3)	
Metastasis Timing	Synchronous	32 (40.0)	
	Metachronous	48 (60.0)	
Laboratory Parameters			
CEA (ng/mL)			6.05 (1-1000)
SII			649.70 (143-4797)
Treatment Characteristics			
Targeted Therapy	No	19 (23.8)	
	Yes	61 (76.3)	
Metastasis Surgery	No	56 (70.0)	
	Yes	24 (30.0)	

ECOG: Eastern Cooperative Oncology Group; CEA: Carcinoembryonic antigen; SII: Systemic immune-inflammation index.

Data are presented as mean±standard deviation, median (minimum–maximum), or n (%). ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen; SII, systemic immune-inflammation index.

Patients had a median age of 64 years (range, 25–81) and a mean age of 62.39±11.01 years. Of the study cohort, 51 patients (63.7%) were male and 29 (36.3%) were female. Based on the ECOG scale, 70 patients (87.5%) were categorized as grade 0, whereas 10 patients (12.5%) were categorized as grade 1. Regarding tumor location, the rectum was the most frequently involved site (40.0%, n=32), followed by the left colon (32.5%, n=26) and the right colon (27.5%, n=22). Histopathological evaluation showed grade 2 tumors in 63 patients (78.8%) and grade 3 tumors in 17 patients (21.2%).

The liver was the predominant site of metastasis, occurring in 44 patients (55.0%), followed by other metastatic sites (26.3%, *n*=21), the lungs (22.5%, *n*=18), and the peritoneum (6.3%, *n*=5). Using our study-specific classification based on the number of metastatic organs, 24 patients (30.0%) had involvement of ≤3 metastatic organs, whereas 56 patients (70.0%) had involvement of ≥4 metastatic organs. Synchronous metastatic disease was observed in 32 patients (40.0%), while 48 patients (60.0%) had metachronous metastases.

The median baseline CEA concentration level was 6.05 ng/mL (range, 1–1000), and the median SII was 649.70 (range, 143–4797). Targeted therapy was administered to 61 patients (76.3%), whereas metastasectomy was performed in 24 patients (30.0%).

The median progression-free survival (PFS) was 21.10 months (range, 3.0–61.9) and the median overall survival (OS) was 42.80 months (range, 4.4–88.7). Disease progression occurred in 56 patients (70.0%), whereas 36 patients (45.0%) died during the follow-up period.

The prognostic value of baseline CEA and SII for OS was assessed using ROC curve analysis. Baseline CEA demonstrated a significant ability to discriminate survival outcomes, with an AUC of 0.699 (95% CI, 0.583–0.816; p=0.002). According to the Youden index, the optimal cutoff value for CEA was 4.65 ng/mL, corresponding to a sensitivity of 80.6% and a specificity of 56.8%. In contrast, SII showed no significant predictive performance for overall survival (AUC, 0.523; 95% CI, 0.392–0.653; p=0.728). The optimal SII cutoff value determined by the Youden index was 826.1, with a sensitivity of 47.2% and a specificity of 65.9%.

Based on these cutoff values, 48 patients (60.0%) were classified as having high baseline CEA (>4.65 ng/mL), whereas 32 (40.0%) had low baseline CEA (≤4.65 ng/mL). High SII (>826.1) was observed in 32 patients (40.0%), while 48 (60.0%) had low SII (≤826.1). According to the combined CEA-SII classification, 28 patients (35.0%) were assigned to Group 0 (low CEA/low SII), 28 (35.0%) to Group 1 (either high CEA or high SII), and 24 (30.0%) to Group 2 (high CEA/high SII) (Table 2).

Kaplan–Meier analysis demonstrated a significant association between baseline CEA levels and OS. Patients with low baseline CEA (≤4.65 ng/mL) experienced a significantly longer median OS than those with high baseline CEA (>4.65 ng/mL). Median OS reached 57.6 months (95% CI, 32.83–82.37) in the low CEA group, compared with 27.4 months (95% CI, 22.12–32.68) in the high CEA group (log-rank, p<0.001) (Fig. 1).

Survival outcomes were further examined after stratification by baseline SII. Patients in the low-SII group (≤826.1) had a median OS of 47.6 months (95% CI, 38.06–57.14), compared with 27.4 months (95% CI, 17.06–37.74) in the high-SII group (>826.1). Despite a trend toward longer survival with low SII, statistical significance was not achieved (log-rank, p=0.051) (Fig. 2).

Table 2. Distribution of CEA, SII, and combined groups based on optimal cut-off values

Variable	Category	Frequency (n)	Valid Percent (%)
CEA Group	Low (≤4.65 ng/mL)	32	40.0
	High (>4.65 ng/mL)	48	60.0
SII Group	Low (≤826.1)	48	60.0
	High (>826.1)	32	40.0
Combined Group	CEA low + SII low (Group 0)	28	35.0
	Either CEA or SII high only (Group 1)	28	35.0
	CEA high + SII high (Group 2)	24	30.0

CEA: Carcinoembryonic antigen; SII: Systemic immune-inflammation index.

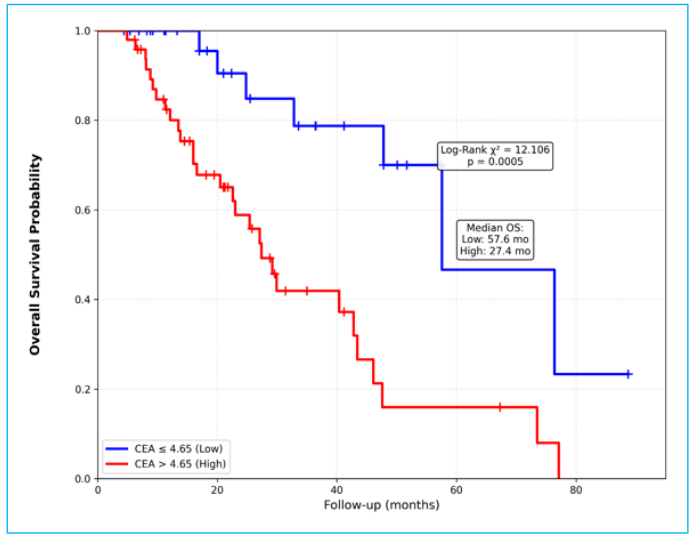

Figure 1. Overall survival (OS) according to CEA.

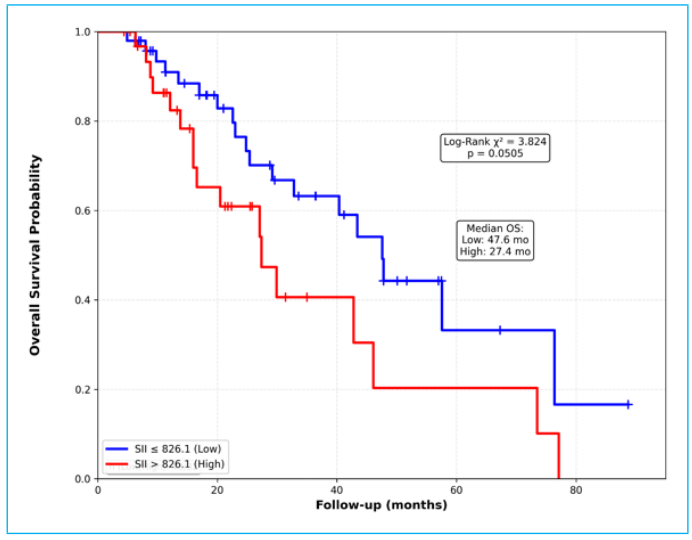

Figure 2. Overall survival (OS) according to SII.

The prognostic value of the combined CEA–SII classification was also evaluated using Kaplan–Meier analysis. Significant differences in OS were observed among the three risk groups (log-rank, p=0.014). Median OS was 57.6 months (95% CI, 40.48–74.72) for Group 0 (low CEA/low SII), 40.4 months (95% CI, 18.83–61.97) for Group 1 (either high CEA or high SII), and 27.4 months (95% CI, 16.43–38.37) for Group 2 (high CEA/high SII). These findings demonstrated a progressive decline in survival with increasing CEA–SII risk category (Fig. 3).

A similar pattern was observed for PFS. Patients with low baseline CEA (≤4.65 ng/mL) experienced longer PFS than those with elevated CEA levels (>4.65 ng/mL). Median PFS was 54.5 months (95% CI, 4.80–104.21) in the low-CEA group and 13.7 months (95% CI, 11.88–15.52) in the high-CEA group (log-rank, p<0.001) (Fig. 4).

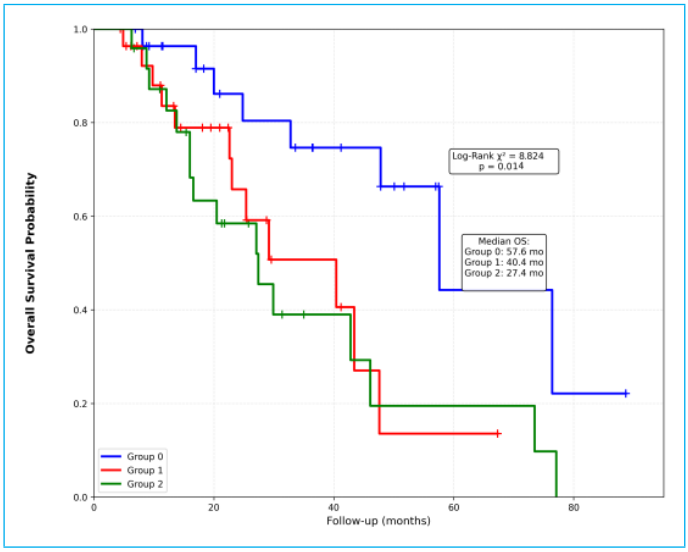

Figure 3. Overall survival (OS) according to combined CEA-SII groups.

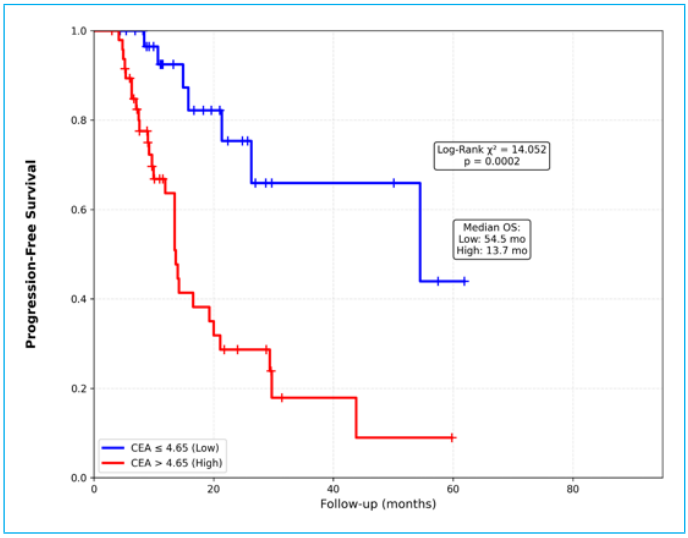

Figure 4. PFS according to CEA.

PFS was also evaluated according to baseline SII. Median PFS was 26.3 months (95% CI, 0.31–52.29) in patients with low SII (≤826.1), versus 14.2 months (95% CI, 10.24–18.16) in those with high SII (>826.1). The difference between the groups was statistically significant (log-rank, p=0.047) (Fig. 5).

Kaplan–Meier analysis according to the combined CEA-SII classification also demonstrated significant differences in PFS among the three prognostic groups (log-rank, *p*=0.008). The median PFS was 54.5 months (95% CI, 3.82–105.18) in Group 0 (low CEA/low SII), 19.3 months (95% CI, 12.20–26.40) in Group 1 (either high CEA or high SII), and 14.0 months (95% CI, 13.00–15.00) in Group 2 (high CEA/high SII) (Fig. 6).

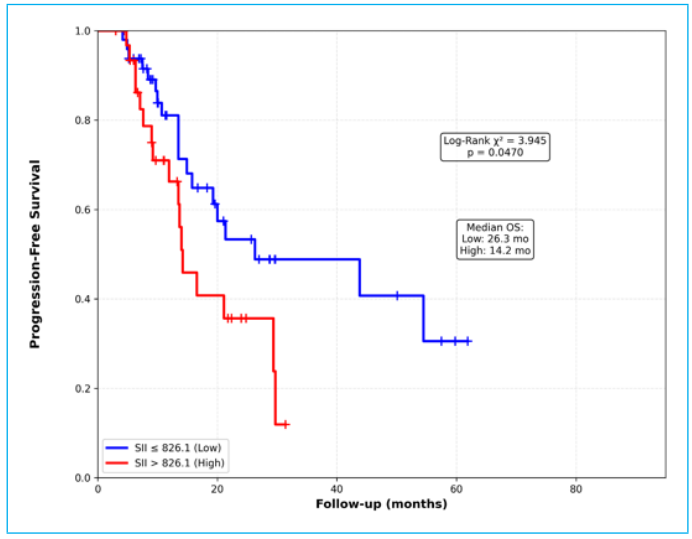

Figure 5. PFS according to SII.

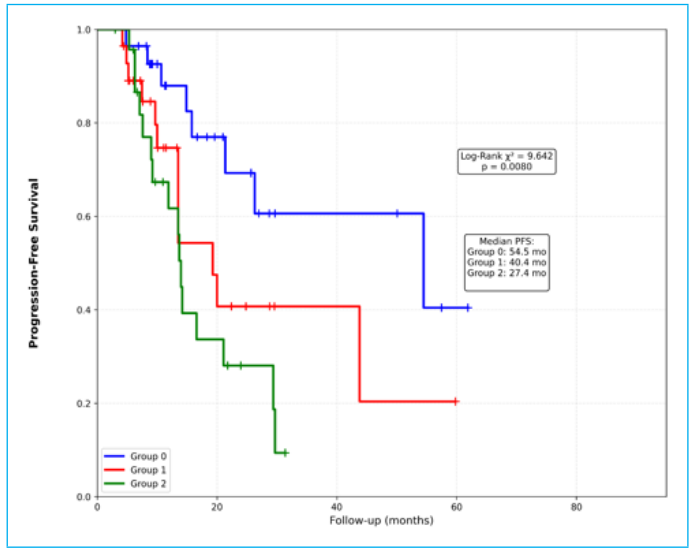

Figure 6. PFS according to combined CEA-SII groups.

Factors associated with OS were evaluated using both univariable and multivariable Cox proportional hazards regression analyses. In the univariable analysis, tumor grade, ECOG performance status, baseline CEA group, and the combined CEA–SII classification were significantly associated with OS. Baseline SII group, timing of metastasis (synchronous vs. metachronous), and metastasectomy showed borderline statistical significance (Table 3).

Because the combined CEA–SII classification was derived from the individual CEA and SII variables, two separate multivariable Cox regression models were developed to avoid multicollinearity. In Model 1, clinical variables were analyzed together with the CEA and SII groups, whereas in Model 2, the combined CEA-SII group was included instead of the individual CEA and SII variables (Table 4).

Table 3. Univariate and multivariate Cox Regression analysis based on OS

Variables	Univariate Level		Multivariate Level	
	HR (95% CI)	p	HR (95% CI)	p
Sex	1.317 (0.628-2.762)	0.466		
Age	1.024 (0.984-1.065)	0.249		
Grade	3.409 (1.530-7.594)	**0.003**	2.973 (1.234-7.165)	**0.015**
Tumor Location	1.086 (0.722-1.633)	0.693		
Metastasis Timing	1.788 (0.919-3.480)	0.087		
Targeted Therapy (Yes vs. No)	0.990 (0.428-2.287)	0.981		
Metastasis Surgery (Yes vs. No)	0.446 (0.195-1.020)	0.056		
ECOG performance status (1 vs. 0)	2.655 (1.087-6.486)	**0.032**	1.978 (.739-5.290)	0.174
CEA Group (High vs. Low)	3.995 (1.728-9.237)	**0.001**	4.717 (1.164-19.117)	**0.030**
SII Group (High vs. Low)	1.922 (0.987-3.741)	0.054		
Combined Group	1.726 (1.163-2.562)	**0.007**	0.887 (0.420-1.871)	0.752

Reference categories were ECOG performance status 0, grade 2, rectum for tumor location, low CEA, low SII, no targeted therapy, no metastasis surgery, and follow-up metastasis for metastasis timing, as applicable. ECOG: Eastern Cooperative Oncology Group; CEA: Carcinoembryonic antigen; SII: Systemic immune-inflammation index.

Table 4. Multivariate Cox Regression Analysis - Model 1 and 2

Variables-Model 1	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)
Grade	1.062	0.448	5.625	1	0.018	2.893	1.203-6.960
ECOG performance status (1 vs. 0)	0.777	0.507	2.351	1	0.125	2.174	0.806-5.869
CEA Group (High vs. Low)	1.302	0.480	7.354	1	0.007	3.676	1.435-9.418
SII Group (High vs. Low)	0.137	0.392	0.123	1	0.726	1.147	0.532-2.472
Variables-Model 2							
Grade	1.021	0.441	5.362	1	0.021	2.776	1.170-6.587
ECOG performance status (1 vs. 0)	0.920	0.487	3.563	1	0.059	2.509	0.965-6.519
Combined Group	0.574	0.212	7.312	1	0.007	1.775	1.171-2.689

Model Statistics:
-2 Log Likelihood: 220.478
Overall Score: $\chi^2 = 23.949$, df = 4, $p < 0.001$
ECOG: Eastern Cooperative Oncology Group; CEA: Carcinoembryonic antigen; SII: Systemic immune-inflammation index.

In Model 1, tumor grade and baseline CEA were identified as independent prognostic factors for OS. Grade 3 disease was associated with nearly a threefold increase in mortality risk relative to grade 2 disease (HR, 2.893; 95% CI, 1.203–6.960; p=0.018). Similarly, patients with elevated baseline CEA (>4.65 ng/mL) had a significantly greater mortality risk than those with lower CEA levels (HR, 3.676; 95% CI, 1.435–9.418; p=0.007). In contrast, baseline SII did not retain independent prognostic significance (HR, 1.147; 95% CI, 0.532–2.472; p=0.726).

In Model 2, both tumor grade and the combined CEA–SII classification independently predicted OS. Moving up by one category in the combined CEA–SII classification was associated with a 77.5% higher risk of death (HR, 1.775; 95% CI, 1.171–2.689; p=0.007). ECOG performance status showed a trend toward statistical significance but did not reach the predefined significance threshold (HR, 2.509; 95% CI, 0.965–6.519; p=0.059).

To identify independent predictors of PFS, Cox regression analyses were conducted in a stepwise approach, with univariable analyses performed first, followed by multivariable modeling. In the univariable analysis, ECOG performance status, tumor grade, metastasectomy, baseline CEA group, and the combined CEA–SII classification were significantly associated with PFS (Table 5).

As in the OS analysis, two distinct multivariable Cox regression models were used to address potential multicollinearity, since the combined CEA–SII classification was derived

Table 5. Univariate and Multivariate Cox Regression Analysis based on PFS

Variables	Univariate Level		Multivariate Level	
	HR (95% CI)	p	HR (95% CI)	p
Sex	1.151 (0.655-2.020)	0.625		
Age	0.997 (0.969-1.027)	0.847		
ECOG performance status (1 vs. 0)	4.043 (1.796-9.102)	**0.001**	2.852 (1.227-6.629)	**0.015**
Grade	2.864 (1.480-5.541)	**0.002**	2.462 (1.243-4.877)	**0.010**
Tumor Location	0.991 (0.712-1.380)	0.956		
Metastasis Timing	1.063 (0.612-1.845)	0.828		
Targeted Therapy (Yes vs. No)	1.663 (0.809-3.417)	0.166		
Metastasis Surgery (Yes vs. No)	0.379 (0.199-0.721)	**0.001**	0.541 (0.272-1.076)	0.080
CEA Group (High vs. Low)	2.473 (1.375-4.447)	**0.002**	2.399 (0.872-6.598)	0.090
SII Group (High vs. Low)	1.491 (0.857-2.596)	0.158		
Combined Group	1.427 (1.031-1.974)	**0.032**	0.842 (0.463-1.532)	0.574

Reference categories were ECOG performance status 0, grade 2, rectum for tumor location, low CEA, low SII, no targeted therapy, no metastasis surgery, and follow-up metastasis for metastasis timing, as applicable. ECOG: Eastern Cooperative Oncology Group; CEA: Carcinoembryonic antigen; SII: Systemic immune-inflammation index.

from the individual CEA and SII variables. In Model 1, clinical variables were analyzed together with the baseline CEA and SII groups, whereas in Model 2, the combined CEA-SII group was included instead of the individual CEA and SII variables (Table 6).

In Model 1, ECOG performance status and tumor grade remained independent prognostic factors for progression-free survival. Each one-point increase in ECOG performance status was associated with a 3.16-fold higher risk of disease progression (HR, 3.157; 95% CI, 1.350–7.383; p=0.008). Similarly, patients with grade 3 tumors had a significantly greater risk of progression than those with grade 2 tumors (HR, 2.359; 95% CI, 1.190–4.676; p=0.014). Metastasectomy (HR, 0.528; 95% CI, 0.265–1.054; p=0.070) and baseline CEA group (HR, 1.803; 95% CI, 0.923–3.521; p=0.085) showed borderline significance, whereas no independent association between baseline SII and PFS was observed in the multivariable analysis (HR, 1.165; 95% CI, 0.636–2.133; p=0.621).

In the second multivariable model, ECOG performance status, tumor grade, and metastasectomy remained independent predictors of PFS. ECOG performance status was associated with a more than threefold increase in the risk of disease progression (HR, 3.274; 95% CI, 1.431–7.492;

Table 6. Multivariate Cox Regression Analysis - Model 1 and 2

Variables-Model 1	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)
ECOG performance status (1 vs. 0)	1.150	0.433	7.038	1	0.008	3.157	1.350-7.383
Grade	0.858	0.349	6.047	1	0.014	2.359	1.190-4.676
Metastasis Surgery (Yes vs. No)	-0.638	0.353	3.275	1	0.070	0.528	0.265-1.054
CEA Group (High vs. Low)	0.589	0.342	2.976	1	0.085	1.803	0.923-3.521
SII Group (High vs. Low)	0.153	0.309	0.244	1	0.621	1.165	0.636-2.133
Variables-Model 2							
ECOG performance status (1 vs. 0)	1.186	0.422	7.887	1	0.005	3.274	1.431-7.492
Grade	0.829	0.344	5.802	1	0.016	2.291	1.167-4.496
Metastasis Surgery (Yes vs. No)	-0.771	0.338	5.187	1	0.023	0.463	0.238-0.898
Combined Group	0.239	0.179	1.777	1	0.183	1.270	0.894-1.806

Model Statistics:
-2 Log Likelihood: 359.370
Overall Score: $\chi^2 = 28.953$, df = 4, $p < 0.001$
ECOG: Eastern Cooperative Oncology Group; CEA: Carcinoembryonic antigen; SII: Systemic immune-inflammation index.

p=0.005), while grade 3 tumors also showed a significantly higher risk of progression than grade 2 tumors (HR, 2.291; 95% CI, 1.167–4.496; p=0.016). Metastasectomy was independently associated with a reduced risk of progression (HR, 0.463; 95% CI, 0.238–0.898; p=0.023). The combined CEA–SII classification showed a significant relationship with PFS in the univariable analysis; however, its prognostic effect did not persist after multivariable adjustment (HR, 1.270; 95% CI, 0.894–1.806; p=0.183).

Discussion

Baseline CEA, SII, and their combined classification were evaluated as prognostic biomarkers in patients with metastatic colorectal cancer. High baseline CEA emerged as an independent predictor of poorer OS, whereas SII alone lost its independent prognostic significance after adjustment for other clinical variables. In contrast, the combined CEA–SII classification offered additional prognostic information for OS, with survival outcomes progressively worsening across increasing risk categories. Although this combined classification was significantly associated with PFS in the Kaplan–Meier analysis, its prognostic value was no longer significant in the multivariable model. Collectively, these findings suggest that integrating a tumor-specific biomarker with a systemic inflammatory marker may improve prognostic stratification in patients with metastatic colorectal cancer.

Baseline CEA demonstrated strong prognostic performance in the present cohort. ROC analysis confirmed its ability to discriminate overall survival, while Kaplan–Meier analysis showed significantly shorter overall and progression-free survival among patients with elevated CEA levels. Moreover, multivariable Cox regression identified high baseline CEA as an independent predictor of mortality, conferring an approximately 3.7-fold higher risk of death. These findings reinforce the clinical utility of baseline CEA as a simple and readily available prognostic biomarker in metastatic colorectal cancer.

CEA remains the most commonly used serum biomarker in colorectal cancer and is strongly associated with tumor burden, disease aggressiveness, and treatment response. Numerous studies have shown that elevated baseline CEA is linked to unfavorable survival outcomes.[9,11–13] Prager et al.[8] reported reduced treatment response and shorter survival in patients receiving bevacizumab-based therapy who had high baseline CEA levels. Likewise, Quidde et al.[12] and Sefrioui et al.[14] demonstrated that baseline CEA provides prognostic information in patients receiving systemic therapy for metastatic colorectal cancer. Our results are in agreement with these observations and further support the clinical value of baseline CEA as a readily available biomarker for prognostic stratification.

The SII, derived from peripheral neutrophil, platelet, and lymphocyte counts, reflects the balance between systemic inflammatory activity and the host immune response. Increasing evidence indicates that cancer-related inflammation contributes to multiple stages of tumor progression, including proliferation, angiogenesis, invasion, and metastatic dissemination.[3,5] Consequently, SII has attracted considerable attention as a simple, inexpensive, and readily available biomarker with potential prognostic value across a broad range of solid tumors.

Several studies have suggested that elevated SII is associated with unfavorable clinical outcomes in colorectal cancer. Recent meta-analyses have consistently demonstrated that patients with high SII experience shorter overall and progression-free survival.[4,15,16] Xie et al.[17] demonstrated that elevated SII independently predicted worse OS in patients with metastatic colorectal cancer, while Shen et al.[18] reported that inflammation-based hematological indices may provide valuable prognostic information in this patient population.

Contrary to previous reports, baseline SII did not emerge as an independent predictor of outcome in our multivariable models. Although higher SII values were associated with shorter PFS on Kaplan–Meier analysis, the relationship was attenuated after accounting for other clinical factors. This discrepancy may have several possible explanations. The modest cohort size may have reduced the ability to detect an independent effect of SII. Furthermore, the biological and clinical heterogeneity inherent in metastatic colorectal cancer means that patient prognosis is shaped by a complex interplay of tumor-related and clinical characteristics, such as primary tumor site, extent of metastatic involvement, treatment approach, and underlying tumor biology. Another consideration is that SII was measured at a single time point before treatment; therefore, dynamic variations in systemic inflammation over the course of therapy could not be examined. Collectively, these findings suggest that SII alone may have limited prognostic utility and that its clinical value is likely enhanced when interpreted alongside established prognostic variables.

An important observation of the present study was the prognostic value of the combined CEA–SII classification for overall survival. Kaplan–Meier analysis demonstrated clear separation of survival curves among the three risk groups, and multivariable Cox regression confirmed that the combined classification remained an independent predictor of overall survival. Specifically, each incremental increase in the CEA–SII risk category corresponded to a 77.5% increase

in mortality risk. Although the combined classification was also significantly associated with progression-free survival in the univariable survival analysis, this finding was no longer observed after adjustment for clinical variables.

The biological rationale for combining CEA and SII lies in the fact that these biomarkers reflect different aspects of the tumor-host interaction. While CEA primarily reflects tumor burden and tumor biology, SII reflects the host immune response and systemic inflammatory status. Therefore, the simultaneous consideration of tumor characteristics and host-related features may offer broader prognostic insight than biomarkers focusing on either component alone.

Evidence regarding the combined use of CEA and inflammation-based biomarkers in metastatic colorectal cancer remains limited. Cai et al.[10] demonstrated that the C-SIRI score, which combines CEA with the systemic inflammation response index, was associated with survival in patients undergoing curative surgery for colorectal cancer. Similarly, Uzunoglu et al.[19] reported significant associations between preoperative CEA and SII levels, advanced TNM stage, and adverse pathological characteristics in patients with sporadic colorectal cancer. However, these investigations primarily involved non-metastatic or surgically treated populations. Consequently, data evaluating the prognostic relevance of the combined CEA–SII assessment specifically in metastatic colorectal cancer are still scarce.[19,20]

The present study has several notable strengths. First, optimal cutoff values for both CEA and SII were established using ROC curve analysis, enabling the development of a novel risk stratification model based on their combined assessment. Second, because the combined CEA–SII classification was derived from the individual CEA and SII variables, two separate multivariable Cox regression models were developed to account for potential multicollinearity while independently assessing the prognostic value of each model. Finally, the use of routinely available and cost-effective laboratory parameters enhances the potential applicability of this prognostic model in daily clinical practice.

Several limitations of the present study warrant consideration. The retrospective nature of the study and its conduct at a single center may have increased the potential for selection bias and restricted the applicability of the results to broader patient populations. The relatively limited cohort size may also have decreased the ability to detect certain associations, particularly in subgroup analyses. Moreover, SII was measured only at the time of metastatic diagnosis, preventing assessment of longitudinal changes in systemic inflammation during treatment. Molecular data on clinically relevant biomarkers, such as RAS and BRAF mutations and microsatellite instability, were also unavailable for evaluation. Further validation in larger, prospective, multicenter cohorts is required to confirm these results and clarify the clinical relevance of the combined CEA–SII classification.

Conclusion

In conclusion, baseline CEA remained independently associated with OS in patients with metastatic colorectal cancer, whereas SII alone did not retain independent prognostic significance. However, integrating CEA with SII improved prognostic stratification for overall survival beyond the use of either biomarker alone. Given that both markers are routinely measured, inexpensive, and readily accessible, this combined approach may represent a practical tool for pretreatment risk assessment in daily oncology practice. Nevertheless, larger prospective multicenter studies are required to validate these findings before their widespread clinical application.

Disclosures

Ethics Committee Approval: The study was approved by the Zonguldak Bülent Ecevit University Non-Interventional Clinical Research Ethics Committee (no: 2026/10, date: 20.05.2026).

Informed Consent: The requirement for informed consent was waived by the Ethics Committee because of the retrospective design of the study.

Conflicts of Interest: The author declared no conflict of interest.

Funding: The author declared that no funding was received for this study.

Use of AI for Writing Assistance: The author declared that no artificial intelligence (AI)–assisted technologies were used in the preparation of this manuscript.

Peer-review: Externally peer-reviewed.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of ıncidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209–49. [CrossRef]
2. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. Lancet 2019;394(10207):1467–80. [CrossRef]
3. Hanahan D. Hallmarks of cancer: new dimensions. Cancer Discov 2022;12(1):31–46. [CrossRef]
4. Menyhart O, Fekete JT, Győrffy B. Inflammation and colorectal cancer: a meta-analysis of the prognostic significance of the systemic immune-inflammation index (SII) and the systemic inflammation response index (SIRI). Int J Mol Sci 2024;25(15):8441. [CrossRef]
5. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res 2014;20(23):6212–22. [CrossRef]

6. Dong M, Shi Y, Yang J, Zhou Q, Lian Y, Wang D, et al. Prognostic and clinicopathological significance of systemic immune-inflammation index in colorectal cancer: a meta-analysis. Ther Adv Med Oncol 2020;12:1758835920937425. [CrossRef]
7. Lakemeyer L, Sander S, Wittau M, Henne-Bruns D, Kornmann M, Lemke J. Diagnostic and prognostic value of CEA and CA19–9 in colorectal cancer. Diseases 2021;9(1):21. [CrossRef]
8. Prager GW, Braemswig KH, Martel A, Unseld M, Heinze G, Brodowicz T, et al. Baseline carcinoembryonic antigen (CEA) serum levels predict bevacizumab-based treatment response in metastatic colorectal cancer. Cancer Sci 2014;105(8):996–1001. [CrossRef]
9. Nicholson BD, Shinkins B, Pathiraja I, Roberts NW, James TJ, Mallett S, et al. Blood CEA levels for detecting recurrent colorectal cancer. Cochrane Database Syst Rev 2015;2015(12):CD011134. [CrossRef]
10. Cai H, Chen Y, Zhang Q, Liu Y, Jia H. High preoperative CEA and systemic inflammation response index (C-SIRI) predict unfavorable survival of resectable colorectal cancer. World J Surg Oncol 2023;21(1):178. [CrossRef]
11. Dawood S, Sirohi B, Shrikhande SV, Toh HC, Eng C. Potential prognostic impact of baseline CEA level and surgery of primary tumor among patients with synchronous stage IV colorectal cancer: a large population based study. Indian J Surg Oncol 2015;6(3):198–206. [CrossRef]
12. Quidde J, Denne L, Kutscheidt A, Kindler M, Kirsch A, Kripp M, et al. Baseline and on-treatment markers determining prognosis of first-line chemotherapy in combination with bevacizumab in patients with metastatic colorectal cancer. Oncol Res Treat 2017;40(1–2):21–6. [CrossRef]
13. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of systemic immune-inflammation index in cancer: A meta-analysis. J Cancer 2018;9(18):3295–302. [CrossRef]
14. Sefrioui D, Beaussire L, Gillibert A, Blanchard F, Toure E, Bazille C, et al. CEA, CA19–9, circulating DNA and circulating tumour cell kinetics in patients treated for metastatic colorectal cancer (mCRC). Br J Cancer 2021;125(5):725–33. [CrossRef]
15. Malik M, Radecka B, Gełej M, Jackowska A, Filipczyk-Cisarż E, Żurowska M, Hetman K, et al. Predictive and prognostic role of systemic immune-inflammation index (SII) in metastatic colorectal cancer patients treated with trifluridine/tipiracil. Biomedicines 2024;12(9):2076. [CrossRef]
16. Tang JN, Goyal H, Yu S, Luo H. Prognostic value of systemic immune-inflammation index (SII) in cancers: a systematic review and meta-analysis. J Lab Precis Med 2018;3:29. [CrossRef]
17. Xie QK, Chen P, Hu WM, Sun P, He WZ, Jiang C, et al. The systemic immune-inflammation index is an independent predictor of survival for metastatic colorectal cancer and its association with the lymphocytic response to the tumor. J Transl Med 2018;16(1):273. [CrossRef]
18. Shen X, Xiang M, Tang J, Xiong G, Zhang K, Xia T, et al. Evaluation of peripheral blood inflammation indexes as prognostic markers for colorectal cancer metastasis. Sci Rep 2024;14(1):20489. [CrossRef]
19. Uzunoglu H, Gul MO, Kina U, Gurleyik MG. Use of the systemic immune inflammation index, TNM classification, and CEA in pre- and post- prognostic evaluation of sporadic colorectal cancer. Ann Ital Chir 2022;92:319–24.
20. Fu J, Zhu J, Du F, Zhang L, Li D, Huang H, et al. Prognostic inflammatory index based on preoperative peripheral blood for predicting the prognosis of colorectal cancer patients. Cancers (Basel) 2020;13(1):3. [CrossRef]